ABSTRACT

Migraine headache is typically characterized by unilateral pain and a cluster of related symptoms that include nausea or sensitivity to light. Approximately 33% of individuals with migraine headache also experience migraine aura—neurologic symptoms, such as speech impairment or visual disturbances, which usually precede the migraine episode by approximately 5 to 20 minutes. Standardized diagnostic criteria for migraine headache with and without aura have been developed by the International Headache Society. Most patients with migraine experience a headache once a week to once a month. Some patients gradually develop a pattern of frequent, and sometimes daily, headaches. Several risk factors for chronic daily headache (CDH) have been identified, including stress, female sex, and several psychiatric and general medical conditions. A pattern of CDH is also observed in many individuals with headache who overuse acute pain relievers. In the past, migraine headache was viewed as primarily a disorder of the cerebral blood vessels. More recent research has established that migraine headache is primarily a neurologic, rather than a vascular, disorder. Many medications have been used to prevent migraine headaches; recently available agents include anti-seizure medications and botulinum toxin type A. The medical literature suggests that preventive therapy should be considered for patients with at least 2 to 4 migraine attacks per month, although treatment must be individualized for each patient based on the degree of disability, the patient’s ability to tolerate acute medications, and comorbid disorders. (Adv Stud Pharm. 2007;4(1):11-14)

CLASSIFICATION OF MIGRAINE HEADACHES

Migraine headache is typically characterized by moderate-to-severe pain that is unilateral, pulsating, aggravated by physical activity, and accompanied by nausea, sensitivity to light (photophobia), and sensitivity to sound (phonophobia). Despite these common features, the presentation of migraine headache may vary considerably from patient to patient. Many patients experience migraine aura, a pattern of reversible neurologic symptoms (eg, visual disturbances or numbness) that usually occur approximately 5 to 20 minutes before the headache begins. Although common, migraine aura is not required for a diagnosis of migraine headache, and most patients with migraine do not have aura. In addition, some people with migraine headache may experience other symptoms that appear as much as 2 days before the migraine headache begins. These symptoms are known as premonitory symptoms and are different from migraine aura. Premonitory symptoms may include fatigue, difficulty concentrating, neck stiffness, nausea, visual disturbances, yawning, and pallor. Approximately 30% of individuals with migraine are able to identify specific migraine triggers—foods, odors, or other factors that can stimulate migraine headaches. Many potential migraine triggers have been identified, including fasting, inadequate sleep, stress, bright lights, certain odors, caffeine, alcohol, foods, and chemicals (including some common food additives, such as aspartame or monosodium glutamate). Even changes in the weather or in altitude can act as migraine triggers. It is a common misperception that migraine headaches must include aura, light sensitivity, and 1-sided pain. In fact, it is not necessary to have all of these symptoms in order to have migraine headaches. For example, one nationwide survey of individuals with migraine headaches in the United States found that only 59% of individuals had 1-sided pain, 36% had migraine aura, and 80% had sensitivity to light.

Definitions for different headache types are described in detail in diagnostic guidelines developed by the International Headache Society (IHS). The original guidelines were published in 1988, and a recent update
and revision of the guidelines was published in 2004. These guidelines note that migraine headache is a complex disorder with many different clinical subtypes. In general, patients with migraine headaches may be divided into 2 broad groups: migraine headaches without aura and migraine headaches with aura. The IHS diagnostic criteria for migraine headache without aura and migraine headache with aura are listed in the Sidebar.1

Migraine headaches are often confused with other headache types, including sinus headache and tension headache. As described in an accompanying article by Richard G. Wenzel, PharmD, most headaches that are attributed to sinus or tension headache are actually migraine.5 The defining characteristic that differentiates migraine from other headache types is disability; migraine headaches nearly always cause significant disability or limitation of normal activities, whereas sinus or tension headaches rarely cause significant disability.6 Migraine headache also may be confused with other severe disabling headache disorders that are actually quite rare. For example, cluster headache may cause significant pain and disability, but has a clinical presentation and typical patient profile that are distinct from migraine headache. Cluster headache is characterized by severe, 1-sided pain that affects the eye or the temple.7 Cluster headaches can occur several times per day and are accompanied by at least 1 of the following: tears or swelling/reddening of the eye, nasal congestion or rhinorrhea, edema of the eyelid, forehead or facial sweating, and pupil constriction or ptosis. Whereas migraine headache is more common among women, cluster headache usually affects men.7

### Predictors of Chronic Headache

Most patients with migraine headaches exhibit a pattern of recurring severe headache episodes and a return to normal functioning between episodes. Approximately 60% of individuals with migraine headache have 1 or more attacks per month, and 25% have 1 or more per week.4 In approximately 20% of cases, migraine headache gradually progresses to a pattern of chronic frequent headaches and continuing neurologic dysfunction between episodes.8 This shift in migraine frequency also is accompanied by increased prevalence of psychologic disorders and muscle pain.9 Chronic headache is often associated with anxiety and depression and with significant impairment of patient quality-of-life ratings.9 Although chronic headaches may be caused by the overuse of acute pain medications, the most recent revision to the IHS headache diagnostic guidelines recognizes chronic migraine (CM) headache (headaches ≥15 times/month for ≥3 months) as a complication of conventional migraine headache and distinct from chronic headaches that are caused by medication overuse.10

One recent long-term study of 450 patients with migraine headaches found that 14% had developed chronic headache after 1 year.11 Risk factors for chronic headache included a high frequency of headaches at baseline, comorbid psychiatric disorders, and high levels of stress. Chronicity also is associated with certain medical conditions, including hypertension, allergies, asthma, arthritis, hypothyroidism, sleep disturbances, and snoring.11,12 High dietary fat intake, obesity, insulin resistance, and cigarette smoking also have been linked to chronic headache.10 Chronic headache is also more common among women than men.12

As noted previously, some cases of chronic headache represent a natural progression of migraine from an earlier stage of intermittent headache to a later stage of more frequent headaches.12 In other cases, chronic headaches are caused by the overuse of analgesics.12 A potential side
effect of the frequent use of pain relievers is a "rebound" headache, which leads to a vicious circle of self-medication with products, such as ibuprofen, naproxen, or acetaminophen, on a daily or near-daily basis to try to treat these near-constant headaches. Preservation and over-the-counter products can cause medication overuse headache (MOH). Chronic headache also has been shown to be increased by high levels of caffeine consumption. Chronic headache that is caused by medication overuse is a significant clinical challenge and requires discontinuation of the patient's pain medications to break the cycle of medication overuse and rebound headache. Some individuals require intravenous treatments to break the cycle of medication overuse and many patients who are overusing pain relievers will eventually relapse.

**Biology of Migraine and Preventive Treatments**

Until the 1980s, it was generally believed that migraine headache was primarily a vascular disorder that was caused by changes to the blood vessels that supply the brain. Subsequent research demonstrated that migraine headache is actually a neurologic disorder that is more closely related to changes within the central nervous system (CNS) than the cerebral blood vessels. Although the details are not completely understood, most experts now believe that the primary mechanism of migraine headache is related to high levels of neural activity that first occurs in the CNS and that results in increased activity in nerve pathways that transmit pain information from a layer of tissue that covers the surface of the brain (the dura). These changes are accompanied by increased activity of sensory nerve fibers from the head and face, which results in the throbbing pain of migraine. It is also believed that these changes in peripheral pain pathways are accompanied by changes within the brain that increase sensitivity to painful stimuli. The causes of the initial heightened brain activity that triggers migraine headache are not known, but may include abnormally low levels of magnesium or of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), abnormally high concentrations of the excitatory neurotransmitter glutamate, alterations in cell membrane ion channels, or other mechanisms.

Several medications have been used for migraine preventive therapy, including β-blockers (ie, propranolol and timolol), tricyclic antidepressants, calcium channel blockers, cyproheptadine, and nonsteroidal anti-inflammatory drugs. In most cases, it is not well understood how these agents produce their effects on migraine frequency and severity. Two relatively recent additions to the list of migraine preventive medications are anti-seizure agents (ie, divalproex sodium and topiramate) and botulinum toxin type A. Anticonvulsants were evaluated for migraine headache prevention after clinicians noted that migraine headache and epilepsy share several features. They tend to occur together, they are periodic in nature, are exacerbated by known (and somewhat overlapping) triggers, are disorders of overactivity of the CNS, and both require long-term preventive therapy. Antiseizure medications may prevent migraine headache by modulating the inhibitory neurotransmitter GABA, although other mechanisms, such as effects on sodium channels or glutamate activity, are also possible. The precise mechanism of action of botulinum toxin type A in migraine headache is not clear, but it may block nerve fibers that transmit pain information in the same manner that it blocks nerve fibers that cause contraction of facial muscles. To date, the only therapies to hold US Food and Drug Administration indication for migraine prevention are propranolol, timolol, divalproex sodium, and topiramate.

**Guidelines for Preventive Therapy**

For patients with frequent, severe migraine attacks, treatment should usually include abortive medications to treat acute migraine attacks and preventive medications to reduce the frequency and severity of future attacks. Acute medications should be taken as soon as possible when a migraine headache begins. In contrast, preventive medications are taken continually to reduce the frequency of migraine headaches and reduce the degree of disability caused by migraine. Preventive medications also may improve the patient's response to acute therapies when migraine headaches occur. The appropriate use of preventive agents also reduces the likelihood that patients will overuse acute pain medications and develop MOH. As noted previously, more frequent headache is a risk factor for migraine chronicity. This suggests that preventive therapies may help to reduce the risk of converting from episodic to CM. In patients who have already developed MOH, removal of the acute pain medications is usually required before preventive agents are effective.

There is no universal standard for the use of preventive medications in patients with migraine headache. Some experts recommend that preventive medications should be considered for patients who have 4 or more migraine episodes per month. However, migraine prophylaxis must be individualized for each patient on the
basis of factors, such as attack severity and the degree of disability.10 For example, some patients may experience significant disability from only 2 to 3 attacks per month.10 According to preventive therapy guidelines developed by the US Headache Consortium, preventive medications also may be considered for patients who have an increasing frequency of migraine attacks, because of patient preference, or because the patient has one of several uncommon headache conditions that require preventive treatments.21 Preventive therapies also may be considered for patients with specific contraindications to acute agents. Triptans, for example, which are used for the acute treatment of migraine headache attacks, cannot be administered during pregnancy because of the risk of fetal harm (pregnancy category C).24 Selecting a preventive agent also requires consideration of comorbid conditions and the potential side effects of treatment. For a patient with comorbid depression, an antidepressant may be helpful for managing depression and migraine prevention. Side effects, such as weight gain or loss of libido, may decrease patient adherence to therapy, even if the treatment is effective. In addition, weight gain may increase the risk of conversion from episodic to CM, as obesity is a significant risk factor for headache chronicity.10

CONCLUSIONS

Migraine headache is a chronic, recurring disorder that is characterized by disabling pain and by neurologic features that include migraine aura, premonitory symptoms, and responsiveness to certain behavioral or environmental triggers. A substantial number of individuals with migraine headache eventually develop a pattern of frequent (in some cases, daily) recurrent headaches and residual neurologic or psychologic dysfunction between episodes. Chronic daily headache may occur as a natural progression from conventional migraine, or it may develop in response to the overuse of pain medications. Preventive medications may be used to reduce the frequency and severity of migraine headache. Migraine prophylaxis must be individualized on the basis of the patient’s headache frequency, degree of disability, adverse reactions associated with acute medication, comorbid conditions, and other factors. Preventive therapies are essential to provide optimal migraine control for many patients with frequent migraine headaches and may prevent the progression of migraine to a daily or near-daily frequency.

REFERENCES