Migraine Update

Diagnosis and Treatment

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ABSTRACT

Migraine is a common intermittently debilitating neurovascular disorder that affects younger adults, especially women. The diagnosis is generally made based on clinical criteria, with neuroimaging used in some cases to exclude secondary causes of headache. This article reviews current understanding of the mechanisms underlying migraine and approaches to treating it.

Migraine is an extraordinarily common, chronic, intermittently disabling, and usually inherited neurovascular disorder. Patients with this condition typically suffer severe headache accompanied by autonomic symptoms, and a minority experience transient neurological symptoms known as an aura. The incidence of migraine peaks between 15 years and 24 years of age,[1] and the prevalence is highest among persons between the ages of 35 and 45 years.[2] In the United States, the one-year prevalence rate of migraine is estimated to be 17.6% in women and 5.7% in men,[2] and the cumulative lifetime incidence of migraine is 43% in women and 18% in men.[1] Evidence suggests that migraine is underdiagnosed. One study reported that one-fourth of patients whose headaches met the criteria for migraine were not diagnosed as having this condition;[3] another found that approximately half of patients with migraine were undiagnosed.[4] Even when diagnosed, migraine is often undertreated.

The frequency, duration, and intensity of migraine attacks can vary from person to person and from episode to episode. The majority of migraine patients experience periods of temporary disability that affect their work and leisure activities and, thus, their productivity and quality of life. This article reviews recent developments in the understanding and treatment of migraine.

Diagnosing Migraine

Evolving diagnostic criteria have facilitated the diagnosis and study of headache in general and migraine in particular.[5,6] Migraine is the most common severe primary headache. It has six subtypes, several of which have subforms (Table 1).[6] The forms of migraine most frequently experienced are migraine without aura, typical aura with migraine headache, and typical aura without headache. In one population study, 64% of patients with migraine had migraine without aura, 18% had migraine with aura, 13% had both types of migraine, and 5% could not be subtyped.[7]

The International Classification of Headache Disorders, Second Edition (ICHD-II) diagnostic criteria for common forms of migraine and typical aura are provided in Table 2.[6] The ICHD-II criteria for migraine and other primary headaches uniformly include "not attributed to another disorder" and recommend that secondary headache disorders suggested by the patient's history and/or physical and/or neurological examinations be excluded by "appropriate investigations." The presence of red, more so than yellow, flags increases the likelihood of a secondary cause of headache and should prompt further evaluation (Table 3).[8]

The probability that a patient has migraine increases with each of the following: asymmetry of pain; throbbing pain; pain that is moderate to severe in intensity; pain that is accompanied by nausea; associated sensitivity to light, sound, and often smell; the presence of typical migraine aura symptoms; and a family history of migraine (found in about two-thirds of patients). Allodynia (a painful response to a stimulus that does not nor-

Table 1

Subtypes and Subforms of Migraine

Migraine without aura

Migraine with aura

- Typical aura with migraine headache
- Typical aura with nonmigraine headache
- Typical aura without headache
- Familial hemiplegic migraine
- Sporadic hemiplegic migraine
- Basilar-type migraine

Childhood periodic syndromes that are commonly precursors of migraine

- Cyclical vomiting
- Abdominal migraine
- Benign paroxysmal vertigo of childhood

Retinal migraine

Complications of migraine

- Chronic migraine
- Status migrainosus
- Persistent aura without infarction
- Migrainous infarction
- Migraine-triggered seizure

Probable migraine

- Probable migraine without aura
- Probable migraine with aura
- Probable chronic migraine

Source: Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Available at: www.ihs-classification.org/en/. Accessed April 15, 2010.

mally produce pain such as light touch or pressure) is also typical during a migraine attack, and its severity tends to correlate with migraine duration, attack frequency, and disability.[9] Migraine headaches without aura tend to be more frequent, more severe, longer-lasting, more disabling, and more likely to become chronic than migraine headaches with aura.

The following three-question screening developed by Lipton et al. can help in diagnosing migraine:[10]

In the last three months, did you have the following with your headaches:

1. You felt nauseated or sick to your stomach?
2. Light bothered you a lot more than when you do not have headaches?
3. Your headaches limited your ability to work, study, or do what you needed to do for at least one day?

If a patient responds positively to two out of the three questions, there is a 93% chance that their headaches are migraine; if all three responses are positive, they have a 98% chance of having migraine headaches. In most patients, migraine can be diagnosed based on clinical criteria. When it cannot or when the patient's presentation suggests the possibility of a secondary cause of headache, the patient should be referred to a neurologist or other headache specialist. Neuroimaging is the best diagnostic tool for excluding most secondary headache disorders. CT imaging is preferred for ruling out acute hemorrhage, fracture, or paranasal sinus disease, while MRI is better if other conditions are suspected. These include infarction, brain

Table 2

Criteria for Diagnosing Migraine

Migraine without aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting four to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

Typical aura with migraine headache

A. At least two attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
   1. Fully reversible visual symptoms including positive features (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
   2. Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
   3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
   1. Homonymous visual symptoms and/or unilateral sensory symptoms
   2. At least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occurring in succession over ≥5 minutes
   3. Each symptom lasting ≥5 and ≤60 minutes
D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or within 60 minutes
E. Not attributed to another disorder

Typical aura without headache is the same as typical aura with migraine headache, except that criterion D is replaced by "Headache does not occur during aura nor follow aura within 60 minutes."

Source: Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Available at: www.ihs-classification.org/en/. Accessed April 15, 2010.

Table 3

Headache Warning Signs

Red Flags

- Head or neck injury
- New onset or new type or worsening pattern of existing headache
- New level of pain (eg, worst ever)
- Abrupt or split-second onset
- Triggered by Valsalva maneuver or cough
- Triggered by exertion
- Triggered by sexual activity (preorgasmic, orgasmic)
- Headache during pregnancy or puerperium
- Age >50 years
- Neurological signs or symptoms (seizures, confusion, impaired alertness, weakness, papilledema, etc.)
- Systemic illness
  - Fever
  - Nuchal rigidity
  - Weight loss
  - Scalp artery tenderness
- Secondary risk factors
  - Cancer
  - Immunocompromised host (HIV, on immunosuppressants, etc.)
  - Recent travel (domestic, foreign)

Yellow Flags

- Wakes patient from sleep at night
- New onset side-locked headaches
- Postural headaches

Source: De Luca GC, Bartleson JD. When and how to investigate the patient with headache. Semin Neurol. 2010;30(2):131-44.

tumors, brain infections, posterior fossa abnormalities including Chiari malformation, low CSF pressure syndrome, pituitary lesions, and craniocervical junction abnormalities.[8] Unfortunately, MRI often shows too much. In a population-based study of 2,000 individuals, MRI detected brain infarcts in 7.2%, cerebral aneurysms in 1.8%, and benign tumors in 1.6%.[11] These incidental findings cause worry and frequently result in additional tests and sometimes treatment, none of which helps the headache for which the diagnostic study was obtained.

Pathophysiology

Migraine can be viewed as an inherited disorder with episodic symptoms that arise in the brain. Sensory input from the trigeminal nerve and the ninth and 10th cranial nerves, humoral factors (eg, blood glucose, ingested food substances, gonadotrophic hormones), environmental factors (eg, too much or too little sleep, stress and release from stress, strong smells, bright lights, and change in barometric pressure), and other factors can trigger attacks.

The brain events that initiate a migraine attack are not well understood. Given the emerging evidence that migraine is based on complex, heterogeneous genetics, migraine attacks may be initiated in several ways. All humans have a trigeminocervical pain system that governs the head and upper neck, serving as a type of early warning system to protect the brain and upper cervical spinal cord from real or threatened injury. Any alteration in the stability of pathways either directly involved in or modulating the trigeminocervical pain system is a potential cause of migraine. Some people may inherit a low activation threshold for migraine; others, a very high activation threshold. The more often destabilizing triggering factors in the environment either separately or in combination meet this threshold, the more often the pain system is activated. This would explain why some people are headache prone and others are headache resistant.

Aura is thought to be caused by a spreading wave of depolarization (cortical spreading depression). Aura is associated with a localized reduction in blood flow followed by an increase in blood flow and characteristically affects the parietooccipital cortex.[12] Experimental evidence suggests that the cortical events underlying aura symptoms may be one of the ways that headaches are initiated in migraine patients. It is likely that the genes that make a person susceptible to aura are distinct from the ones that confer susceptibility to migraine headaches.

We are just beginning to identify the genes underlying migraine. Three different abnormal genes have been discovered in separate kindreds who suffer from familial hemiplegic migraine, a relatively rare and severe subform of migraine accompanied by motor weakness. The mutations relate to ion channel function and neuronal hyperexcitability.[13]

There also have been reports of an increased occurrence of patent foramen ovale (PFO) in patients with migraine with aura and possibly migraine without aura. There also have been anecdotal reports that PFO closure results in a reduced frequency of migraine attacks.[14] It is postulated that microemboli or humoral factors pass through the PFO, bypass the lungs, and trigger a migraine.

Treatment

There are three broad approaches for treating patients with migraine: avoidance of recognized triggers; prompt treatment of acute attacks; and preventive antimigraine therapy. These three approaches can and should be combined, if needed.

■ Avoiding Migraine Triggers

Many factors have been associated with the provocation of migraine attacks (Table 4). Patients should be advised to analyze their headaches to see if they can identify anything that triggers them. Keeping a headache diary or calendar can help in this regard. It may take up to 24 hours for a trigger to provoke a migraine attack.

Patients should, of course, avoid headache triggers if they can. However, this may not always be possible for three reasons: the majority of migraine attacks are not triggered, many known migraine triggers are unavoidable (eg, menstruation, a change in the weather, stress), and migraine triggers are often variable in their ability to cause an attack.

■ Acute Treatment

For most patients, the mainstay of migraine therapy is prompt treatment of the acute attack with a medication that is effective for them. A number of drugs are available for treating patients who experience migraine attacks.

Triptans. The development of triptans during the last 20 years has been a remarkable achievement. Triptans offer benefits to patients with migraine that are similar in magnitude to the benefit levodopa provides to patients with Parkinson's disease. There are seven different triptans (Table 5). All are 5-$HT_{1B/1D}$ receptor agonists. The potential mechanisms of action include cranial vasoconstriction and inhibition of peripheral and central trigeminal nerve transmission.[15] All triptans are available in pill form. Only one can be administered by injection (sumatriptan), two are available as a nasal spray (sumatriptan and zolmitriptan), and two are available in an oral-dissolving tablet (rizatriptan and zolmitriptan).

Triptans reverse nausea and pain while leaving the patient clear-headed; they also are nonaddictive. Triptans provide substantial headache relief in up to three-fourths of patients. Many patients who have menstrually associated migraine attacks can be successfully treated with a triptan. In general, almotriptan, eletriptan, and rizatriptan are probably the most effective triptans. Almotriptan, frovatriptan, and naratriptan have fewer side effects. Rizatriptan and zolmitriptan are associated with more nausea.[16-18]

Side effects of triptans include tingling, flushing, and sensations of warmth, heaviness, pressure, or tightness in different parts of the body including the chest and neck. Triptans can constrict the coronary arteries and in rare instances may cause myocardial ischemia. They are contraindicated in patients with ischemic

Table 4

Common Migraine Triggers

- Fasting
- Alcoholic beverages
- Hormonal therapy
- Caffeine withdrawal
- Stress or release from stress
- Too much or too little sleep
- Menstruation
- Fatigue
- Exposure to bright lights, loud noises, smoke, and strong scents
- Change in the weather
- Acute head injury
- Foodstuffs including:
  - Chocolate
  - Aged cheeses
  - Processed meats
  - Fermented foods
  - Aspartame
  - Monosodium glutamate
  - Citrus fruits
  - Nuts

Table 5

Currently Available Triptans

Triptan	Medication form and strength (mg) (usual optimum dose is in bold)	Recommended dosage interval (≥ hours)	Maximal daily dosage (mg/24 hours)
Almotriptan (Axert)	Tablet, 6.25, **12.5**	2	25
Eletriptan (Relpax)	Tablet, 20, **40**	2	80
Frovatriptan (Frova)	Tablet, **2.5**	2	7.5
Naratriptan (Amerge)	Tablet, 1, **2.5**	4	5
Rizatriptan (Maxalt)	Tablet, 5, **10**	2	30
	Oral disintegrating tablet, 5, **10**	2	30
Sumatriptan (Imitrex)	Tablet, 25, **50**, 100	2	200
	Nasal spray, 5, **20**	2	40
	Subcutaneous, **6**	1	12
Sumatriptan 85 mg + naproxen 500 mg (Treximet)	One fixed-dose tablet	2	2 tablets
Zolmitriptan (Zomig)	Tablet, **2.5**, 5	2	10
	Oral disintegrating tablet, **2.5**, 5	2	10
	Nasal spray, **5**	2	10

heart disease, uncontrolled hypertension, cerebrovascular disease, peripheral vascular disease, or hemiplegic or basilar migraine.[15,18] They are compatible with most other medications. However, patients who are using selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) should be cautioned to watch for symptoms of serotonin syndrome. If a patient does not respond to one triptan, he or she may respond to another. An adequate trial of triptan therapy should include trying at least two different triptans for two migraine attacks each.

Dihydroergotamine. Dihydroergotamine (DHE) is an old drug that is still useful for some patients with severe migraine. One-half to 1 mg can be injected subcutaneously, intramuscularly, or intravenously, and the dose can be administered a total of three times in 24 hours. DHE is also available as a nasal spray and may soon be released in an orally inhaled form. DHE is also a 5-$HT_{1B/1D}$ receptor agonist and cannot be used within 24 hours of taking a triptan. It has the same contraindications as triptans, and it should not be used by women who are pregnant or nursing. Ergotamine tartrate is also an ergot, but it is rarely used because it is associated with more side effects and is not widely available.

Other Drugs. In addition to migraine-specific drugs such as triptans and DHE, there are multiple single-ingredient and multi-ingredient, over-the-counter and prescription analgesics that are helpful to individuals who experience milder attacks and for whom migraine-specific drugs are unhelpful or contraindicated. These include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, weak and strong opioid analgesics, and combinations of these drugs. Triptans also can be combined with another analgesic such as a NSAID. In this regard, there is a new formulation of sumatriptan called Treximet, which contains 85 mg of sumatriptan and 500 mg of naproxen in each tablet. Alternatively, the patient could be directed to take any triptan with an over-the-counter NSAID.

Considerations for Acute Treatment. When treating an acute attack, it is critical that patients take their medication as soon as the headache begins. Patients almost universally report that if they can catch the headache early, they are much more likely to reduce its intensity and duration. Many also find that rest, especially in a dark room, can be helpful in stopping an acute migraine attack. Unfortunately, many patients with migraine wait in an effort to avoid taking their medication and/or with the hope that this time will be different. Medications may fail to work if the patient takes them too late, takes too low a dose, has expectations that are too high, or experiences early vomiting that prevents absorption. Also, patients may experience relief from their headache but still have nausea or bothersome medication side effects; or they may experience headache recurrence.

Because acute treatment can fail, it can be helpful for the patient to have a rescue treatment to use when their standard

treatments do not work. This might include an outpatient injection of an opioid or ketorolac with an adjuvant or antinauseant. One of three treatment options may be used to break up a protracted migraine attack: intravenous DHE, intravenous valproate sodium (Depacon), or a short course of corticosteroids.

Although many patients experience only occasional migraine attacks that are mild or easily treated, some patients develop frequent or even daily headaches. The ICHD-II recognizes chronic migraine as a specific diagnosis when patients experience headaches at least 15 days per month for at least three months, and more than half of their headaches meet criteria for migraine without aura.[6,19] In some patients, progression of their migraine from episodic to chronic is associated with the frequent use of simple and multi-ingredient analgesics or acute antimigraine drugs. Caffeine consumption can cause the same phenomenon. The risk of medication overuse is higher with opioid analgesics and butalbital.[20] Because of the risk of progression as a result of medication overuse, it is recommended that any acute treatment not be used more than two days per week and that butalbital and opioid-containing analgesics not be used more than once a week.

Nausea and vomiting are frequent migraine accompaniments and also can occur as a side effect of the medications used to treat it. It may be helpful to treat patients who have nausea and vomiting with an antiemetic such as prochlorperazine, chlorpromazine, or promethazine administered by mouth or rectum, or metoclopramide by mouth. Antiemetics can be used in combination with analgesic and acute antimigraine medications. If the patient has early vomiting with their migraine attacks, consider using an acute medication that can be administered by injection, nasal spray, or oral-dissolving tablet in order to bypass the stomach or reduce the chance of vomiting.

■ Preventive Treatment

If the frequency, duration, and severity of the patient's migraine attacks are bad enough, consideration should be given to preventive therapy in which medications are given on a regular basis whether or not the patient has a headache. Guidelines for the use of preventive therapy include: when a patient has more than four to six headache days per month; when symptomatic medications are contraindicated or ineffective; when acute medication is required more than twice a week; and for rare types of migraine including hemiplegic migraine, basilar migraine, migraine with prolonged aura, and migraine associated with cerebral infarction. Preventive therapy also should be considered for individuals whose migraine attacks could affect their safety or livelihood (eg, a pilot or professional athlete).

In the case of women who experience migraine attacks exclusively before or during menses, cyclic preventive treatment with an anti-inflammatory drug, transcutaneous estrogen, or twice-daily frovatriptan or naratriptan can be given during the perimenstrual period.[21] If a woman's migraine headaches are severe enough, she can be treated continuously with a preventive medication.

Evidenced-based guidelines for the use of acute and preventive anti-migraine therapy are available.[22,23] The commonly used preventive antimigraine medications are listed in Table 6. In general, a preventive agent is started at a low dose and gradually increased over time until the patient sees benefit, experiences side effects, or reaches the maximal dose. These medications take a minimum of three to four weeks and can take as long as eight to 12 weeks to become effective. They are rarely 100% effective in preventing migraine attacks; a 50% reduction in headache burden is considered a good result and can often be achieved. In general, one preventive medication is used at a time, but combinations of two or more drugs can have added benefit. A combination of a tricyclic agent and a beta blocker or verapamil has been suggested for refractory patients.

A preventive agent is chosen or avoided because of its potential benefit or adverse effect on the patient's other medi-

Table 6

Commonly Used Preventive Antimigraine Medications

Drug	Initial daily dose (mg)	Target daily dose (mg)	Common side effects
Amitriptyline and Nortriptyline	10 or 25	25 to 150	Weight gain, dry mouth, sedation, constipation
Propranolol	60 to 80	120 to 240	Depression, fatigue, hypotension, bradycardia
Atenolol	25	50 to 100	Depression, fatigue, hypotension, bradycardia
Verapamil	80 to 160	240 to 480	Edema, constipation, hypotension
Gabapentin	300	900 to 2,700	Edema, sedation, fatigue, dizziness
Topiramate	15 to 25	100 to 200	Paresthesias, mental slowing, weight loss, kidney stones
Divalproex sodium	250 to 500	750 to 1500	Alopecia, weight gain, nausea, tremor
Botulinum toxin A (Circumferential scalp muscle injections repeated at ≥3-month intervals)	Not applicable	Not applicable	Excessive weakness in facial or upper cervical muscle, ptosis

cal conditions. Patient input is important, especially regarding feelings about side effects. If beneficial, the preventive treatment is usually given for six to 12 months, at which time the need for continuing the drug is reassessed.

Preventive treatments can fail because the starting dose was too high and the patient experienced side effects; the dose was advanced too quickly and side effects occurred; the dose was not pushed high enough; the trial was too short; the patient was not satisfied with the results; or the patient was in a cycle of rebound headaches because of medication overuse when preventive therapy is less likely to be helpful.

New and Future Directions

In addition to new combinations of old drugs (eg, Treximet) and new formulations of old drugs (eg, inhaled DHE), new acute and preventive treatments are being developed for migraine. These include telcagepant, a calcitonin gene-related peptide receptor antagonist, which has undergone phase III trials as an acute treatment.[24]

Established treatments for other neurologic conditions (eg, memantine, which is used for Alzheimer's disease) are being tried for the prevention of refractory migraine.[25]

Because of the possible connection between migraine and PFO, a national, randomized, sham-controlled trial of percutaneous closure of PFOs in patients with frequent and severe migraine attacks who do not respond to preventive treatment is being conducted by AGA Medical Corporation in Plymouth, Minnesota. Abbott Northwestern Hospital, Central Minnesota Heart Center at St. Cloud Hospital, and Mayo Clinic are participating in this trial. Occipital nerve stimulation is also being tried for the treatment of several intractable primary headache disorders including migraine.[26]

As is the case with many other areas of medicine, research is being conducted to find the genes responsible for migraine. Researchers from Mayo Clinic are collecting genomic data on 4,500 patients who have migraine with and without aura and on gender- and age-matched controls. This genomic information will be correlated with headache phenotype, response to acute therapies, response to preventive treatments, and medication side effects.

Conclusion

Migraine is a common condition that is responsible for frequent episodes of temporary disability. Migraine is underdiagnosed and, even when recognized, is frequently undertreated. This is unfortunate because effective treatment is available. Recognition and elimination of migraine triggers can be helpful to some patients. Immediate treatment of an acute migraine attack is the mainstay of treatment for most patients. If the patient's headache burden is severe enough, preventive antimigraine therapy may be appropriate. Patients should be encouraged to track their headaches in order to optimize management of their migraine attacks. **MM**

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