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DEFINITION

Migraine is the most common form of headache that results in medical evaluation and treatment. It is present in roughly 10% to 20% of the population and is seen in about 5% of children.[1] The gender ratio for migraine in children is about 1:1, with a slight preponderance of boys under 12 years of age. After 12 years of age, the incidence of migraine increases in females. Approximately 50% of all migraines begin before the age of 20 years. Migraine occurrence is considered to occur in four phases. First is the prodrome, which is a set of symptoms including mental, neurologic, and other medical changes, such as excessive thirst or feeling cold, that occurs for hours or even days before the headache. The next phase, which is referred to as the aura, is a set of neurologic features and can include changes to vision, sensation, strength, and language that typically last for 5 to 20 minutes and immediately precede the headache. However, many people do not necessarily get a prodrome or an aura before the migraine headache. Migraine headache that followed the aura was previously classified as classic migraine, and migraine without the aura was classified as common migraine, but the current system classifies the two as migraine with or without aura, respectively. Of note, a migraine aura in isolation can be a perplexing symptom complex to the clinician. The headache of migraine can last for hours to days with associated features of sensitivity to light, sound, smell, and motion and it can also include dizziness, neck pain, and a myriad of other symptoms. The headache itself can be on one side (60%) or the whole head (40%), and is typically pounding in nature though this can vary. It is not unusual for a migraine to produce nausea and vomiting and be totally incapacitating and disabling.

The International Headache Society currently classifies headaches into two categories. Primary Headaches are those that cannot be attributed to a specific organic cause or lesion and Secondary Headaches are due to a specific cause.[2] This classification system is endorsed by the World Health Organization. Primary Headaches are divided into four main categories: 1) migraine and its subtypes; 2) tension-type headache; 3) cluster headache and trigeminal autonomic cephalgias; and 4) a miscellaneous category, which includes cough headache, exertional headache, headache associated with sexual activity, hemicrania continua, and a newer diagnosis, new daily persistent headache. Secondary Headaches include eight broad categories: 1) due to head and neck injury; 2) due to vascular abnormalities; 3) due to nonascular intracranial abnormalities, such as neoplasm, epileptic seizure, and abnormal cerebral spinal fluid pressure; 4) due to chemical substances or their withdrawal, 5) due to infections; 6) due to metabolic disorders or homeostatic abnormalities, such as high-altitude, hypertension, or fasting; 7) due to abnormality of the cranium, eyes, ears, sinuses, mouth, or neck; and 8) due to a psychiatric disorder.

SYNONYMS: headache, migraine with aura, migraine without aura, classic migraine, common migraine.

NEUROBIOLOGY OF MIGRAINE

The brain is an electrochemical organ bathed by blood, so theories of migraine etiology will consequentially be described from these perspectives. An overlap across these conceptual mechanisms is becoming clear, with similar phenomena being described with differing functional methods.

ELECTRICAL THEORIES

Many kinds of scalp-level electroencephalographic abnormalities have been described in association with migraine, including generalized, abnormal slow waves, convulsive patterns, and focal abnormalities, and there has been little agreement across the findings as to the incidence of the patterns or their relevance.[3] At the level of the cerebral cortex, an observation of "spreading depression" can be ascribed to Leao's measurement of a change in ongoing activity from exposed cortex during an actual migraine and calculation of the rate of spread across the cortex at about 3 mm/minute.[4] More recently, measurement of brains' neuromagnetic fields have demonstrated abnormality, such as a neuromagnetic wave of excitation followed by depressed slower waves in its wake.[5] The fact that some form of electrical disturbance is present in migraine cannot be doubted, but the exact nature of the disturbance is still unclear and may be understood as epiphenomena of the neurovascular theories.

CHEMICAL THEORIES

Chemical theories of migraine have been attractive due to the apparent parasympathetic qualities (or sympathetic hypofunctional qualities) of migraine, namely dilation of vessels, nausea, miosis, blood pressure aberrations, as well as vegetative symptomatology, depression, hypotonia, and drowsiness. Moreover, parasympathetic inhibitors aborting migraine symptoms have a long history. Though early theories of histamine and acetylcholine in relation to migraine had been discarded, the use of methylsergide, a 5-HT2 agonist, as a preventative agent prompted Sicuteri to propose serotonin as important factor, and this became the basis of modern migraine chemical theory.[6] There are over 300 known serotonin receptor subtypes in the brain and these are divided into three major types, 5-HT1, 2, and 3, each of which has multiple subtypes. The subtypes 5-HT1(b) and 5-HT1(d) cause vasoconstriction and are the target for the group of medications that are collectively termed "triptans," which are the most successful and widely prescribed abortive medications for migraine. Although the brain's serotonin synthesis is within the brainstem's raphe nucleus, there is wide variation in the effects of serotonin because of the various serotonin receptor subtypes and their varied distribution throughout the central nervous system (CNS). This explains the varied effects of "serotonin" medications from treatment of depression, to migraine prophylaxis, to migraine abortion through

cerebral vasoconstriction. In addition to serotonin, neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP), are now also implicated in migraine. These create pain and interact with the brain's vascular system to cause vasodilatation (expansion) and plasma extravasation, which then in turn causes more neurogenic inflammation and vascular dilation.

VASCULAR THEORIES

Though the vasomotor theories can be ascribed to Latham postulating an initial vasoconstrictor phase followed by a vasodilatory phase, the vasomotor theories for migraine are most associated with Wolff. Wolff's experiments demonstrated that the intensity and duration of migraine headache was proportional to the dilation of extracranial vasculature with subsequent neurogenic inflammation and that the headache responsiveness to vasoconstrictors also was related to these cerebral changes.[7] Olsen was able to measure a wave of diminished cerebral blood flow called "oligemia" using radioactive tracers moving in a caudal to rostral direction beginning in the occipital cortex and which persisted after the aura phase for an hour or more.[8] In the next decade, blood flow studies with positron emission tomography demonstrated similar changes in blood flow during migraine with aura.[9]

HORMONAL THEORIES

Migraine is significantly affected by changes in ovarian hormones such as during menarche, pregnancy, and menopause, and exacerbations of migraine are quite common during the periods of rapidly dropping estrogen levels during ovulation and menstruation. Estrogen and progesterone can be either alleviating or exacerbating of migraine, depending on the situation, absolute levels, route, formulation, and consistency of hormone exposure.[10,11] Though ovarian steroids readily pass through the blood brain barrier, neurosteroids are now known to be produced in the brain, and they have direct effects and a role in metabolizing steroids in the brain. Overall, steroids exert their influence in the brain through both genomic and nongenomic mechanisms that have effect durations lasting hours to days, and profound effects on the serotonergic, noradrenergic, glutamatergic, GABAergic, and opiatergic systems. The effect of these ovarian hormones in the CNS may be regional or even neuron specific. Precipitous drops in estrogen, such as during ovulation and menstruation, lead to a decrease in serotonin receptors and serotonin production with inhibition of the main vasoconstrictor mechanism of the CNS and increasing CGRP pain-related neuromodulators. In combination, this significantly lowers the threshold for a migraine event.

GENETIC THEORIES

There has been an explosion of information regarding genetics in migraines in recent years. Most recently, missense mutations in *ATP1A2*, which is a chromosome 1q23 gene that encodes a Na+, K+-ATPase, have been identified as a responsible for familial hemiplegic migraine (FHM).[12] *ATP1A2* is similar in its brain expression to *CACNA1A*, a voltage-gated calcium channel gene that is the first identified hemiplegic migraine gene (FHM1).[13] The shared hemiplegic migraine phenotype for these two genes raises the possibility that they coordinate or regulate ion homeostasis that determines susceptibility to the initiation of both migraine aura and the pain phase of migraine. For the more common and genetically complex forms of migraine, genome-wide screens have identified several new loci on 4q24, 6p12.2–21.1, 11q24, and 14q21.2-q22.3, suggesting additional migraine genes or susceptibility genes in these regions.[14–16] In addition, a recent large, case-control association study has linked single nucleotide polymorphisms in the insulin receptor/INSR gene with migraine.[17,18]

LABORATORY TESTING

Testing is not routinely used in migraine evaluation; however, neuroimaging may be relevant in excluding intracranial pathology for headaches with or without focal neurologic features, or in conditions in which focal neurologic complaints without concomitant headache may be a presenting feature. Head CT is helpful to evaluate for intracerebral bleeds, hypertensive hemorrhage, aneurysmal bleeds, cerebral amyloidosis, masses, edema, or hydrocephalus. Brain MRI offers the advantage of recognizing white matter lesions that may represent migraine vasculopathy but can frequently be confused with stroke or the lesion of multiple sclerosis. Neuroimaging and erythrocyte sedimentation rate should be strongly considered in all patients with new onset headache over the age of 60 to evaluate for temporal arteritis. Cerebral angiography, conventional or magnetic resonance angiography can be helpful to evaluate for cerebral venous sinus thrombosis. A lumbar puncture should be reserved for situations in which encephalitis, meningitis, or abnormality of cerebrospinal fluid pressure is suspected.

DIFFERENTIAL DIAGNOSIS

The timing of symptoms, as well as the quality, location, severity, and exacerbating and alleviating factors is critical to diagnosis migraine. Migraine pain will typically last for hours or days and will be disabling and commonly associated with neurovascular features such as nausea, vomiting, light, and sound sensitivity. Motion sensitivity with headache is thought to be sensitive and specific to migraine. The complex neurologic auras that can occur typically 20 to 30 minutes prior to the headache but which can persist, or recur or occur in isolation without the headache are commonly mistaken for stroke, multiple sclerosis, focal seizure, or psychiatric disease. Autonomic dysfunction associated with migraine can manifest as arrhythmias, presyncope, syncope, and seizures or focal cranial dysautonomia such as Horner's Syndrome. However, each of these other diagnoses should be considered for some patients presenting with what may be migraine.

The International Headache Society's broad and comprehensive scheme for the classification of headaches is useful for both clinical and scientific purposes.[2] Clinicians may use the scheme to reach a specific headache diagnosis and then use that diagnosis to initiate evidence-based treatments for that headache type. In contrast, treatment without the use of a specific diagnosis can lead to ineffective management. Many patients who present to physicians without headache expertise are mistakenly diagnosed with tension headache and this may lead to suboptimal but initially effective treatment. For example, the abortive agent that includes butalbital, acetaminophen, and caffeine often improves headache control acutely but introduces a risk for medication overuse syndrome, previously known as analgesic rebound headache. The majority of patients who seek medical attention for headache have migraine, so are particularly vulnerable to developing medication overuse syndrome. As such, a common recommendation is not to begin a barbiturate and nonsteroidal anti-inflammatory medication until a specific headache diagnosis has been identified.

MANAGEMENT AND TREATMENT

AVOIDANCE OF TRIGGERS

The common migraine triggers are numerous and an exhaustive list of possible migraine triggers is so long as to not be practical, because triggers vary widely among patients and may be idiosyncratic. If attention is paid to tracking timing and frequency of migraines and noting possible triggers, a patient may minimize headache frequency or severity can commonly be achieved with the avoidance of the identified triggers. However, environmental triggers, such as drops in barometric pressure and allergens, are common and inherently more difficult to avoid. Dietary triggers are the most amenable to manipulation and this can be very successful in many patients. Common triggers include monosodium glutamate, which is commonly present in preserved foods and in some ingredients used for freshly prepared foods. Tyramine, a vasoactive peptide found in wine and aged cheese, and nitrates, a vasodilator found in most processed meats, also are food triggers. An extensive list of triggers is beyond the scope of this chapter and can be found at the National Headache Association website (www.headaches.org/content/headache-sufferers-diet). Hormonal changes are potent triggers for migraine, particularly for women, and the use of oral contraceptives will exacerbate migraine in the majority of patients. Hormones and migraine is discussed in more depth in the section on hormonal theories. General wellness, which includes proper nutrition, exercise, regular and adequate sleep, and minimized stress, all have a role in migraine treatment, but these lifestyle factors can be especially difficult to maintain, especially in the younger patient population.

PROPHYLACTIC TREATMENTS

PHARMACEUTICAL APPROACHES

The American Headache Society and American Academy of Neurology recommend that individuals who have excessive headache days each month should be considered for a preventative or prophylactic treatment.[19,20] This is typically a medication that has been shown to reduce the frequency of migraine. Methylsergide was the first agent to be found to reduce migraine frequency, but it is no longer commonly used for this due to adverse effects, such as retroperitoneal fibrosis. Tricyclic antidepressants, such as amitriptyline and nortriptyline, are standard preventative treatments because of their efficacy, once nightly dosing, and low cost, but their anticholinergic adverse effects, such as sedation, dry mouth, and constipation, have limited their use. Monoamine oxidase inhibitor (MAOI) antidepressants, such as phenelzine, can be very effective for migraine prevention, but they are not commonly prescribed because of the risk for hypertensive crisis in patients who cannot adhere to the strict dietary restrictions that MAOI treatment requires. The older, nonspecific beta-blockers, such as propranolol and atenolol, are effective for prevention, but they can cause insomnia, memory loss, loss of libido, and should be avoided in patients with diabetes who are prone to hypoglycemia. Calcium channel blockers have also been recommended and, recently, angiotensin receptor blockers have been shown to be beneficial. Several antiseizure medications are commonly used in clinical practice for the prevention of migraine. Topiramate is the most commonly used antiseizure medication for migraine, and its popularity is due to both its efficacy and weight-loss side effect. Its adverse effects include word finding difficulties, paresthesias, and increased risk of nephrolithiasis. Valproic acid is another effective antiseizure medication for migraine prevention, but its adverse effects of hair loss, weight gain, polycystic ovarian syndrome, and teratogenicity have diminished its used in modern practice. Botulinum toxin injection is indicated when more than 15 migraines occur monthly. The injections are delivered according to a specific 30-point cranial protocol and can be very effective in the most refractive patient. Dosing is typically repeated every 3 months and several dosing sessions are sometimes needed to realize the full efficacy. Botulinum toxin's cost and lack of ease of use limit its utility.

NURTICEUTICAL AND NONPHARMACEUTICAL APPROACHES

Patient preferences or intolerance of prescription treatments have the option of several treatments that are recommended by the AHA based positive studies. Magnesium is the most beneficial of the nonpharmaceutical approaches and it safe for both pediatric and pregnant patients. The authors have found that this is best tolerated in the magnesium malate and magnesium gluconate forms. Both riboflavin and co-enzyme Q10 are each effective for some patients. The herbal remedy butterbur has demonstrated some efficacy in studies, but another herbal remedy, feverfew, has not. Biofeedback has been studied for many years and can benefit some migraine patients, but the lack of standardized protocols and techniques of administration limit the reproducibility of results and the generation of specific treatment protocols. This and poor access issues limit its use in clinical practice. Mindfulness-based stress reduction, yoga, and acupuncture all may benefit some patients, but large, controlled, blinded trials are lacking.

ABORTIVE TREATMENTS

PHARMACEUTICAL ABORTIVE TREATMENTS

Treatments for acute migraine headache can be traced back centuries through opioid analgesics and caffeine to trepanation, which involves drilling or cutting a hole in the skull. With the discovery of ergotamine, a potent vasoconstrictor that is particularly helpful in aborting migraine headache, the vasomotor theory for migraine advanced and scientific inquiry into migraine treatment provided more rapid progress. The only United States Food and Drug Administration approved pharmacologic treatments for acute migraine headache are the triptan agents, which are potent 5HT1b/1d agonists that act to vasoconstrict the cerebral circulation and reduce neurogenic inflammation associated with migraine. There are seven agents currently available, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Patients vary in which is optimal and multiple formulations are available. In particular, sumatriptan is available in delivery preparations that are oral, nasal, subcutaneous injection, and a battery operated patch. Triptans in general are significantly more efficacious when used very early with the onset of headache and are contraindicated in those patients with significant cardiovascular disease and those with complex neurologic features such as hemiplegic migraine.

Though low and high dose potency narcotics may have a role in migraine, they should be used judiciously because scientific efficacy is lacking, and issues such as dependence, habituation, and diversion outweigh their benefit. Butorphanol, a mixed mu receptor agonist/antagonist may have a role for migraine breakthrough pain, or when triptans are either not tolerated or contraindicated. Its use can avert an emergency room visit for injectable narcotics. Because butorphanol is a mixed mu receptor agonist/antagonist it may precipitate dysesthesias and even withdrawal in a narcotic-dependent patient.

DEVICES USED IN TREATMENT

Transcranial magnetic stimulation is approved for the use of migraine but is not commonly utilized because of cost and limited

availability. Transcranial low-output electric stimulation through a device that allows self-administration has also been approved for the use in migraine. Stimulation is delivered daily for 20 minutes. A low response rate over placebo and poor tolerance relegates this approach to secondary or adjunctive treatment.

SURGICAL AND INTERVENTIONAL TREATMENTS

Occipital nerve blocks, typically with bupivacaine and triamcinolone, can be helpful for certain migraine patients and this treatment can also help differentiate migraine from occipital neuralgia. The use of lesionectomy is beginning to find its way into clinical practice.

TREATMENT OF STATUS MIGRAINOSUS

Status migrainosus is defined as a debilitating migraine that lasts more than 72 hours.[2] Such patients typically receive outpatient treatment initially and then may require hospitalization. Treatments aim to break a cycle of recurring headache and commonly include some combination of the following: intravenous hydration; dihydroergotamine, a potent vasoconstrictor that is given either as injections or continuous infusion; intravenous valproic acid; intravenous magnesium; high-dose intravenous steroids, such as methylprednisolone; and high potency narcotics. Hospitalization for status migranosus usually lasts 1 to 5 days.

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ADDITIONAL RESOURCES

www.headaches.org/content/headache-sufferers-diet
https://www.aan.com/Guidelines/Home/GetGuidelineContent/538
https://www.aan.com/Guidelines/Home/GetGuidelineContent/545