Migraine Diagnosis and Pathophysiology

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ABSTRACT

Purpose of Review: This article describes current knowledge regarding headache, especially migraine, and includes information on genetics, anatomy, pathophysiology, and pharmacology in order to demonstrate their relevance to clinical phenomenology.

Recent Findings: Animal models show that drugs effective in migraine prevention may work by raising the threshold for initiating cortical spreading depression and may also attenuate the response to simulation.

Summary: Great advances have been made in diagnosing and understanding migraine over the past several decades. Tools such as the International Classification of Headache Disorders assist in making diagnoses. Although blood vessel changes do occur in migraine, they are not timelocked to the occurrence of head pain. Cortical spreading depression is at least one trigger for the events that occur in migraine. Migraine may be due to the interplay of host susceptibility and various triggers. Nitric oxide and calcitonin gene-related peptide are important mediators, and estrogen seems to ''ramp up'' the system.

Continuum Lifelong Learning Neurol 2012;18(4):753–763.

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Relationship Disclosure: Dr Ward serves as a consultant for Cowan and Company and the US Department of Justice Vaccine Injury Compensation Program and has served as a medicolegal consultant for the State of New Hampshire and the University of Vermont. Dr Ward serves as editor of *Headache Currents*. Dr Ward served as a local investigator for a study sponsored by GlaxoSmithKline for which his institution received funding.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Ward discusses the unlabeled use of amitriptyline for migraine prevention.

INTRODUCTION

Scientific advances over the past several decades have allowed physicians to identify correlations between the clinical features of migraine and changes in the brain and have improved the diagnostic accuracy for migraine (as well as for many other types of headache). To help understand these advances, the history, neuroanatomy, genetics, epidemiology, physiology, and pharmacology of migraine need to be considered. The debate as to whether migraine is primarily a vascular or a neural abnormality has largely been settled. Vascular changes represent an epiphenomenon, and migraine is best thought of as a disorder of brain excitability and sensory dysmodulation causing head pain plus associated features. Migraine is usually a hereditary brain abnormality, although it can occur in other settings, such as after head trauma. Understanding hereditary brain alterations allows for the optimization of treatment of patients with migraines and for the advancement of knowledge regarding the underlying CNS abnormalities that constitute migraine. This article discusses migraine diagnosis and what is known about migraine as an episodic state of altered brain function. Some unanswered questions relevant to the field of headache are also addressed.

MIGRAINE DIAGNOSIS

Although originally developed to ensure uniformity of diagnosis to assist with research in the headache field, the International Classification of Headache Disorders, now in its second iteration (ICHD-II) and about to be updated as ICHD-III, has brought greater clarity to the field of headache diagnosis and is extremely helpful in the clinical arena as well.[1] Indeed, a working knowledge

KEY POINTS

- Headache is a symptom with many potential causes, and the International Classification of Headache Disorders, Second Edition, provides diagnostic criteria, which are useful in making a precise diagnosis.
- Patients with migraines have hyperexcitable brains, and these abnormalities are present both ictally and interictally. These patients have low brain magnesium levels and do not accommodate to repetitive stimuli.

of the ICHD is very useful for optimal patient care. The ICHD is available online and is continuously updated.[2] Headache is a symptom, and the clinician's task is to determine precisely which type of headache(s) a patient has. There are hundreds of causes of headache, some secondary (ie, due to an underlying cause) and others primary (ie, sui generis, no underlying cause).

Migraine is a primary headache disorder and may occur with or without aura. *Aura* is a suboptimal term because it can occur before or during the headache, in the absence of a headache, or in association with other headache types. The word *migraine* comes from the Greek *hemi* and *kranion*, and while migraine is often hemicranial, it is bilateral in about 40% of adults and 60% of children. It is a recurrent disorder often associated with sensory symptoms (photophobia, phonophobia, and osmophobia), nausea or vomiting, and disability (**Table 1-1**).[1,3] Migraines may be characterized as episodic (occurring fewer than 15 days per month) or chronic (occurring 15 days or more per month). Clinically, patients with migraines may seem normal between attacks. Even interictally, however, patients with migraines have abnormalities of brain function that can be shown by tests of contingent negative variation and transcranial magnetic stimulation. They have hyperexcitable brains and do not habituate to normal stimuli.

Migraine aura occurs in only about 20% of patients with migraines. The most common manifestation is visual, often an enlarging scotoma with a shimmering edge (fortification spectra or teichopsia). Patients may also see stars, dots, wavy lines, complex patterns, shapes, or visual distortions. Less common are sensory auras, such as the cheiro-oral aura. In this type of aura, paresthesia begins in the hand and slowly, over minutes, ascends to the shoulder and then may spread to the ipsilateral face

TABLE 1-1 Migraine Without Aura[a]

Description: Recurrent headache disorder manifesting in attacks lasting 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

Diagnostic Criteria:

A. At least 5 attacks fulfilling criteria B through D
B. Headache attacks lasting 4 to 72 hours[b] (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

[a] Adapted from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2004, with permission of SAGE. *cep.sagepub.com/content/24/1_suppl/9.long*.
[b] In children, attacks may last 1 to 72 hours (although the evidence for untreated durations of less than 2 hours in children requires corroboration by prospective diary studies).

and even the inside of the mouth and the tongue. Still less common are auras causing hemiparesis or hemiplegia, and if dominant frontal or temporal lobes are involved, the aura may manifest as a speech disturbance (**Table 1-2**).[1] In 1941, Lashley[4] observed the progression of his own migraine visual aura and deduced that the phenomenon must be moving across his occipital cortex at a rate of about 3 mm/min. Nearly contemporaneously, at Harvard, Leão[5] reported on the phenomenon of cortical spreading depression (CSD) in rabbits. As will be discussed, CSD is importantly linked to migraine phenomenology and helps explain some of the clinical features of this condition.

Migraine is a very common disorder. The cumulative lifetime prevalence is about 43% in women and 18% in men.[6] While migraine occurs about equally in boys and girls (4% to 5%), once puberty occurs it becomes twice as prevalent in females and even more prevalent by middle age. Estrogen plays an important role. Migraine is usually hereditary, and the inheritance is polygenic, although studying the rare monogenic forms (autosomal dominant with high penetrance) may provide information about migraine in general.[7,8] Trauma can also precipitate headache with migrainous features, and the pathophysiologic consequences of head trauma have many similarities to migraine.[9]

Migraine also has many characteristic triggers. It may be viewed as the interaction of environmental triggers and a susceptible host. Migraine triggers include exertion, dietary factors (including delaying a meal), sleep disturbances, head trauma, hormonal influences, and medications. Sometimes these triggers influence nitric oxide (NO), which is involved in migraine pathogenesis.[10]

A number of medical conditions have been shown to be comorbid with

KEY POINTS

- Cortical spreading depression appears to be the underlying phenomenon causing auras, although it may occur in silent areas of the brain as well. Imaging studies such as fMRI and PET have shown this phenomenon.
- Estrogen appears to influence nitric oxide (NO) levels and may partially explain why migraines become more prevalent in women at puberty and even more prevalent by middle age. Estrogen increases NO synthase activity; women have higher NO levels that fluctuate with the menstrual cycle and men have lower levels that do not fluctuate.

TABLE 1-2 Typical Aura With Migraine Headache[a]

Description: Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than 1 hour, a mix of positive and negative features, and complete reversibility characterize the aura, which is associated with a headache fulfilling criteria for migraine without aura.

Diagnostic Criteria:

A. At least 2 attacks fulfilling criteria B through 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 (eg, loss of vision)
   2. Fully reversible sensory symptoms including positive features (eg, pins and needles) and/or negative features (eg, 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 develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
   3. Each symptom lasts ≥5 minutes and ≤60 minutes
D. Headache fulfilling criteria B through D for migraine without aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

[a] Adapted from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2004, with permission of SAGE. *cep.sagepub.com/content/24/1_suppl/9.long*.

KEY POINT

- While blood vessel changes have long been recognized in migraine, they do not and cannot account for all the clinical phenomenology that occurs in this condition. The head pain and vessel caliber changes do not occur at the same time, drugs that do not have vasoconstrictive activity may be effective in migraine, and blood vessel changes do not explain other features of migraine such as inability to accommodate to repetitive stimuli.

migraine, ie, they occur with migraine more frequently than would be expected based on their rates of occurrence individually in the population. These conditions include mitral valve prolapse, Raynaud phenomenon, stroke, epilepsy, and several psychiatric conditions (eg, depression, anxiety, bipolar disorder, and social phobias). Studying the association between migraine and these conditions may provide insights into the underlying mechanisms of migraine.[11]

Migraine was once thought to be primarily a disorder of blood vessels. Advances in knowledge involving genetics, epidemiology, clinical observations, pharmacology, neuroimaging, and physiology have shown that the clinical manifestations of migraine cannot be accounted for simply by changes in blood vessels. Migraine is an abnormal state of the brain. Vascular changes occur, but they are not primary, and while some now prefer to call migraine a neurovascular disorder, there is ample evidence that patients with migraines have an abnormal CNS, resulting in various well-recognized clinical symptoms.[12]

HISTORY

In 1938, Graham and Wolff[13] published an article that significantly influenced thinking about migraine for decades. They demonstrated that the decreased amplitude of arterial pulsations coincided with the reduction of headache pain when IV ergotamine, a vasoconstrictor, was administered during a migraine attack. It became dogma that migraine aura was due to vasoconstriction, and it was thought that the headache was due to vasodilation. It is now recognized that ergotamine (and the triptans) have many actions beyond simply affecting the blood vessel diameter.[14,15] Nonetheless, the debate about the role of blood vessels has influenced research and thinking about migraine pathophysiology for years.

Shortly after Graham and Wolff published their study, Leão[5] reported on CSD, a phenomenon that occurs in lissencephalic animals. CSD, a wave of neuronal depolarization followed by a suppression of neuronal activity with corresponding blood flow changes (hyperemia followed by oligemia), moved across the cerebral cortex at rate of about 3 mm/min. This seemed similar to the phenomenon Lashley[4] reported regarding his own visual aura. CSD can be provoked by chemical, electrical, and mechanical stimuli. It also can occur in the setting of energy failure.[16] EEG can show this phenomenon in lissencephalic animal models but not in the convoluted human brain. Substantial research has shown that CSD plays an important, but not exclusive, role in the genesis of a migraine attack. A more sophisticated understanding of the genesis of migraine encompasses knowledge of the anatomic pathways involving head pain, neurotransmitters and pharmacology, neuroimaging findings, and neurophysiology both during and between migraine attacks.

ANATOMY OF HEAD PAIN

The brain parenchyma is insensate. However, the dura mater, dural vessels, extracranial vessels, proximal cerebral arteries, venous sinuses, cranial nerves (CNs) (III, IV, V, VII, IX, and X), upper cervical roots, cervical muscles and tendons, face, eyes, ears, scalp, oropharynx, and nasal sinuses are innervated and can be painful. Intracranial contents above the tentorium cerebelli are innervated by the trigeminal nerve, and those structures below are innervated by C2, C3, CN VII, CN IX, and CN X. The term *trigeminovascular system* is often used. The dura mater and vessels supplying the meninges have both sensory and autonomic innervation. Unmyelinated C fibers that innervate the peripheral

structures pass through the gasserian ganglion, enter the pons, and run down to the trigeminal nucleus caudalis (TNC). The TNC runs from the medulla down into the region of the third cervical segment where it blends gradually into the cervical dorsal horns. The caudal segment extent varies widely. Some refer to this region as the *trigeminocervical complex*. Fibers from upper cervical roots enter the TNC, which sends fibers rostrally to the thalamus and collaterals to the autonomic nuclei in the brainstem and the hypothalamus. Thalamic neurons project to the somatosensory cortex but also to areas of the limbic system. The TNC also has polysynaptic connections to the parasympathetic superior salivatory nucleus (SSN) in the pons. This nucleus runs through the sphenopalatine (pterygopalatine) ganglion via the greater superficial petrosal nerve and innervates meningeal vessels and the contents of the nasal sinuses and eyes.[17,18]

The TNC can be considered a structure of anatomic and physiologic convergence. Pain from the face and head may be referred to the neck, and pain from the neck can be referred to the face, especially in the distribution of the first division of the trigeminal nerve (V1). The ipsilateral greater occipital nerve, formed by C2, is often tender during an attack of migraine (or during a cluster headache), and neural blockade (an occipital nerve block) at that site may terminate an acute attack.

The periaqueductal gray in the midbrain has connections with the TNC and is known to exert inhibitory influences on that structure. This region of the midbrain has been shown to become activated during a migraine attack, and this activity persists even after the pain has been relieved.

MIGRAINE PATHOPHYSIOLOGY

Clinicians have long recognized that some patients have certain triggers that are repeatedly associated with an attack. These include glare, loud noise, certain odors, certain foods (or delaying a meal), hormonal changes, head trauma, and NO. Also, hours to days before an attack some patients may feel irritable, have food cravings, or experience fatigue or excessive yawning. These premonitory symptoms may be recognized by some patients as suggesting an impending attack. Such symptoms cannot be explained by blood vessels constricting or dilating and instead suggest hypothalamic involvement.[7]

CSD can be a migraine trigger. CSD occurs in the cerebral cortex, cerebellum, and hippocampus. Intracellular calcium rises and calcium waves propagate through glia, affecting vascular activity. As the wave of depolarization moves across the cerebral cortex, NO, arachidonic acid, protons (H+), and potassium (K+) are released extracellularly. Matrix metalloprotease is activated, which may affect the blood-brain barrier. Meningeal nociceptors are activated. Mast cells are activated and degranulate. The trigeminovascular reflex is activated. Trigeminal neurons supplying the dural vessels release calcitonin gene-related peptide (CGRP), substance P, and neurokinin A. The vessels dilate and become inflamed, and plasma protein extravasation occurs (also known as *sterile neurogenic inflammation*). At this point, the first-order trigeminal neuron has been activated (peripheral sensitization) and carries pain signals centrally. The patient may experience pounding pain and pain with head movement. Through its polysynaptic connections with the SSN, a trigeminoparasympathetic reflex may occur, and parasympathetic fibers innervating the dural vessels release acetylcholine, NO, and vasoactive intestinal polypeptide. Clinically, the patient may develop miosis, ptosis, a red eye, lacrimation, and nasal stuffiness or rhinorrhea. Increased

KEY POINT

- The trigeminovascular system linking the fifth cranial nerve territory and the upper cervical region via the trigeminal nucleus caudalis (TNC) explains pain referred between the face and the neck. Polysynaptic connections between the TNC and the superior salivatory nucleus in the lower pons explain the occurrence of ipsilateral autonomic phenomena such as red eye, lacrimation, pupillary inequality, and rhinorrhea during some headache attacks.

KEY POINT

■ Activation of the trigeminovascular system causes peripheral sensitization of the first-order neuron innervating dural blood vessels, which explains the pounding pain. With prolonged duration, second- and third-order neurons become activated, potentially resulting in central sensitization.

CGRP is found in the jugular veins of patients with migraines during an attack (**Figure 1-1**).[7,16,18]

If treated during the early stages of an attack when only peripheral sensitization has occurred, the migraine may be terminated fully. If the attack progresses further, second- and third-order neurons may be activated (trigeminothalamic and thalamocortical). This is called *central sensitization* and involves the phenomenon known as wind-up. Glutamatergic and NO transmission are involved. The clinical manifestation of central sensitization is cutaneous allodynia. The patient may report scalp tenderness and facial, neck, or even extremity pain occurring spontaneously or in response to nonpainful stimuli. Patients may even report that their hair hurts. Once central sensitization has occurred, the attack is much harder to treat, and triptan drugs, such as sumatriptan, may no longer work. However, nonsteroidal anti-inflammatory drugs (NSAIDs) and dihydroergotamine may

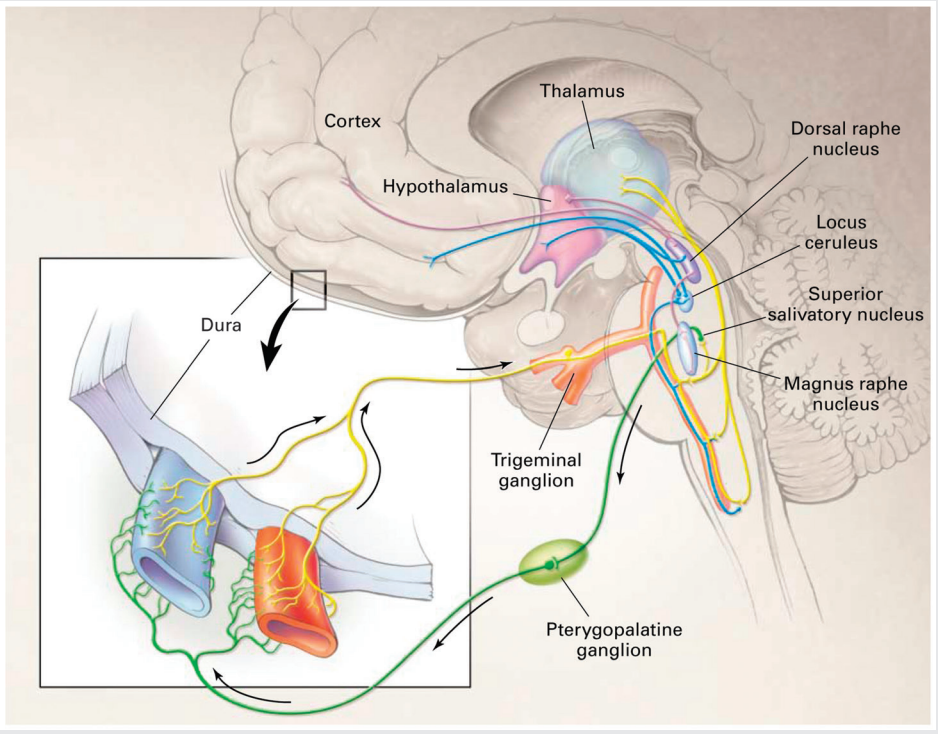

FIGURE 1-1 Pathophysiology of migraine. Migraine involves dysfunction of brainstem pathways that normally modulate sensory input. The key pathway for the pain is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex. In turn, these neurons project through the trigeminothalamic tract, and, after decussating in the brainstem, form synapses with neurons in the thalamus. A reflex connection exists between neurons in the pons and neurons in the superior salivatory nucleus, which results in a cranial parasympathetic outflow that is mediated through the pterygopalatine, otic, and carotid ganglia. This trigeminal autonomic reflex is present in people who do not experience migraines and is expressed most strongly in patients with trigeminal autonomic cephalalgias, such as cluster headache and paroxysmal hemicrania; it may be active in migraine. Brain imaging studies suggest that important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus ceruleus, and nucleus raphe magnus.

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still be effective. Central sensitization is more likely to occur as the duration of an attack increases and is also more likely to be present in chronic migraine than episodic migraine.[8,19,20]

Although only about 20% of patients report a clinical aura, CSD may be occurring in patients without a clinically obvious aura and in ''silent'' areas of the brain. For example, one patient who did not manifest a typical aura (reported only blurry vision) had evidence of abnormal PET activity that appeared to move across the occipital cortex at a rate of about 3 mm/min during a migraine attack, suggestive of CSD.[21]

GENETICS

Migraine is typically hereditary, although the condition is usually polygenic. Advances in understanding the underlying biochemical changes have been made possible in part by studying the rare monogenic forms causing familial hemiplegic migraine (FHM). FHM conditions are autosomal dominant with a high degree of penetrance. Multiple abnormal genotypes have been identified, but they all result in the same clinical phenotype. Some are linked to other paroxysmal neurologic disorders, such as ataxia (eg, episodic ataxia type 6) and seizures. These abnormalities make the migraine brain more susceptible to CSDs.

FHM1, the first disorder identified, is characterized by increased calcium (Ca++) influx into presynaptic terminals due to mutated P/Q-type calcium channels. This results in an increase of function with an increase in extracellular K+ and an increase in glutamate release. FHM2 is characterized by a loss-of-function abnormality that involves the Na+/K+ adenosine triphosphatase, resulting in decreased clearance of synaptic glutamate and K+ by astrocytes. FHM3 is characterized by a gain-of-function mutation involving the voltage-gated sodium channels, also resulting in increased glutamate release. Another known mutation involves the glutamate transporter EAAT1 and is associated with episodic ataxia, seizures, and hemiplegic migraine.[7,8,22]

Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes syndrome (MELAS) is due to a mutation in the mitochondrially encoded NADH dehydrogenase 4 gene, *MT-ND4*, and results in a disturbance in synaptic energy metabolism. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is due to a mutation in the notch 3 gene, *NOTCH3*.[22] Clinically, patients often present in younger years with migraine with aura, in middle age with infarcts, and in old age with dementia.

Additionally, patients with migraines have low brain magnesium levels.[23] Magnesium is an inhibitory ion that plugs calcium channels and tends to inhibit CSD. Knock-in mice with FHM1 have a lower threshold for triggering CSD, and when it occurs it propagates across the cortex at an enhanced rate.[24] Female animals with this abnormality are even more susceptible to CSD than males.[7,25]

The result of these genetic alterations is a hyperexcitable brain. Migraine appears to be an interaction between environmental factors (triggers) and genetic susceptibility. Clinically, patients with migraines have brain abnormalities both during and between attacks. They have a lower threshold for the provocation of visual phosphenes by transcranial magnetic stimulation, they do not habituate to repetitive stimuli, and they show abnormalities in event-related potentials.[26–28]

PHARMACOLOGY

As stated earlier, the antimigraine benefits of ergotamine were originally

KEY POINT

- Central sensitization occurs when second-order (trigeminothalamic) and third-order (thalamocortical) neurons are activated. This process involves glutamate release. Once this occurs, triptan drugs are less likely to work, although nonsteroidal anti-inflammatory drugs and dihydroergotamine may still be effective. Central sensitization is more frequently seen in chronic migraine than episodic migraine.

thought to be solely due to vasoconstriction. While ergot drugs such as ergotamine tartrate and methysergide, as well as the triptans (of which sumatriptan can be considered the prototype), are undoubtedly vasoconstrictive, NSAIDs and CGRP antagonists are effective during migraine attacks in the absence of vasoconstrictive effects.[28,29] It is now appreciated that ergot drugs are active at many receptor sites, some of which affect neurotransmitter release. Some of these sites are the same ones at which triptan drugs (eg, sumatriptan) are primarily active, the 5-hydroxytryptamine 1D and 1B (5-HT_{1D}, 5-HT_{1B}) receptors. The 5-HT_{1D} receptors are presynaptic and are located on trigeminal neurons and elsewhere, including in the TNC. Agonism of 5-HT_{1D} receptors on trigeminal neurons innervating the meninges prevents the release of CGRP. Stimulation of 5-HT_{1B} receptors located on blood vessels causes vasoconstriction. Stimulation of these receptors in the TNC decreases central neuronal signaling (**Figure 1-2**).[18,28]

The triptan drugs were developed in part because of the recognition of the importance of serotonin in migraine pathogenesis.[30,31] At the start of a migraine attack, blood serotonin levels decrease and levels of its metabolite 5-hydroxyindoleacetic acid (5-HIAA) rise.[32] Drugs that deplete serotonin such as reserpine worsen migraine and cause depression. Administration of serotonin (5-HT) during a migraine attack can abort the attack but can cause side effects reminiscent of carcinoid syndrome. The triptan drugs are essentially modifications of the serotonin molecule.

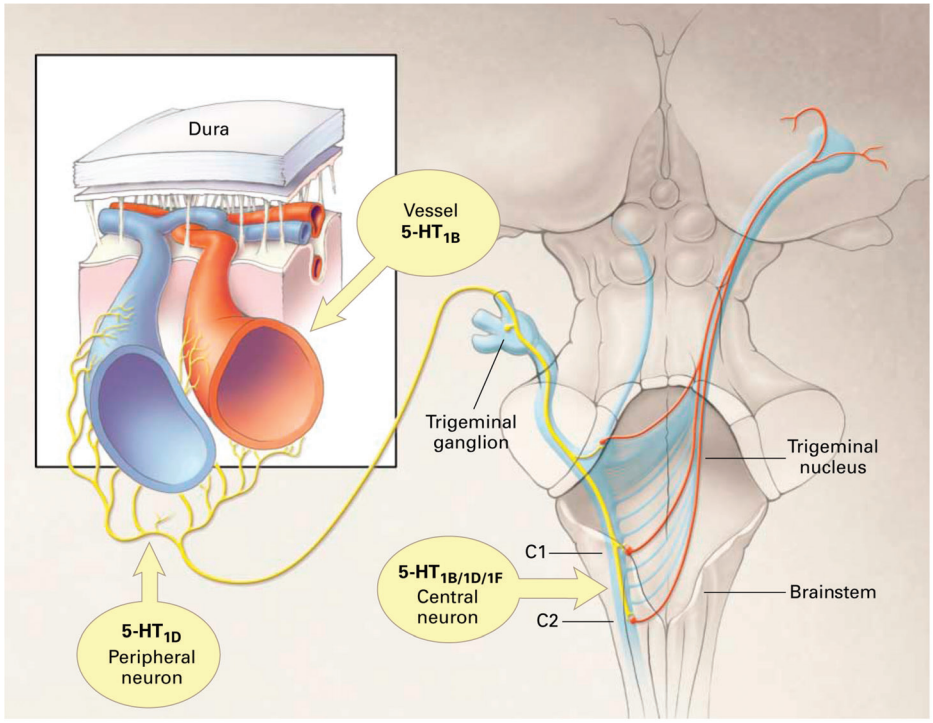

FIGURE 1-2 Possible sites of action of triptans in the trigeminovascular system. 5-HT_{1B} = 5-hydroxytryptamine 1B; 5-HT_{1D} = 5-hydroxytryptamine 1D.

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Animal studies have demonstrated that drugs known to be effective at preventing migraines raise the threshold for initiating CSD and tend to diminish the number of CSD events that occur once the phenomenon is triggered. This effect increases with the duration of drug administration. The suppression of CSD activity has been shown to occur with topiramate, valproate, amitriptyline, methysergide, and DL-propranolol, all drugs known to be clinically effective migraine prophylactics. D-propranolol, which is ineffective clinically, was also ineffective in this animal model.[33]

Estrogen stimulates NO synthase activity. Women have higher circulating NO levels than men, and these levels fluctuate with the menstrual cycle.[10] This fluctuation may explain why migraine prevalence increases dramatically in women after menarche and rises further during the peak reproductive years, declining toward male levels after menopause (**Case 1-1**).

NEUROIMAGING

Various types of headaches have distinctive patterns on PET and fMRI imaging. In migraines, the midbrain and the dorsal pons become active.[28,34] These areas presumably represent activity in the periaqueductal gray and the locus ceruleus (which controls cerebral blood flow). Additionally, patients with migraines, particularly those who have migraine with aura, may display white matter abnormalities visible on T2-weighted and fluid-attenuated inversion recovery MRI images, so-called unidentified bright objects.[35] Some of these lesions persist and have

KEY POINT

- If animal studies are a valid surrogate, drugs that act to prevent migraines seem to raise the threshold for initiating cortical spreading depression and, once initiated, attenuate the response. These drugs seem to be more effective with longer duration of treatment.

Case 1-1

A 41-year-old woman began having migraine attacks at the age of 14, shortly after her menarche. Triggers for these attacks included her menses, ovulation, and delaying a meal. One or two days before her attacks she would feel fatigued and yawn excessively. Before some of her more severe episodes she would experience an enlarging visual scotoma with a shimmering edge lasting for 20 to 30 minutes, followed by a unilateral pounding headache with nausea and sometimes vomiting. If she was unsuccessful in treating the attack, it might last 2 to 3 days and she would have to lie in a dark, quiet room. She has learned that treating as soon as possible during a migraine offers her the best chance of success.
Her mother had similar attacks as does one of her two daughters. When her obstetrician/gynecologist prescribed an estrogen-containing oral contraceptive she experienced an increase in the frequency and severity of her migraine attacks leading her to stop the medication.

Comment. This patient had the onset of headaches near the time of her menarche. Estrogen is known to stimulate nitric oxide synthase, which results in higher nitric oxide levels. She had other triggers besides her menses and was aware of them. She also had a prodrome of yawning (a hypothalamic phenomenon that cannot be ascribed to a vascular etiology, but rather is dopaminergic). Sometimes she would manifest a visual aura, presumably due to cortical spreading depression traveling across her occipital cortex. Her attacks met ICHD-II criteria for migraine with and without aura. She had learned she would get a better result if she treated early (before central sensitization could occur). As is the case for many women, additional estrogen given as an oral contraceptive worsened her headache tendency; this also often occurs with hormone replacement therapy.

been considered infarcts, whereas others seem to be transient.[36,37] Typically these lesions are subclinical and have no obvious clinical correlate.

OTHER ABNORMALITIES

Patent foramen ovale (PFO) occurs in about 25% of the general population but in about 50% of patients with migraine with aura. The significance of this finding is unclear, but it has been speculated that the right-to-left shunt may circumvent the usual filtering function of the lung and allow microemboli or possibly various chemical transmitters such as serotonin to affect intracranial blood vessels, perhaps triggering CSD and migraine attacks. A recent clinical trial addressed closure of PFO in patients with migraine and showed no benefit. However, the trial design and methodology have been criticized, so this remains an area of controversy.[38] It has been hypothesized that the cerebral blood vessels may be affected by the loss of pulmonary filtering and, coming full circle, the role of blood vessels has again been suggested.[7]

CONCLUSION

Migraine is a common clinical disorder that is generally hereditary. The brain in patients with migraines is hyperexcitable, with a lower threshold for the initiation of CSD, which activates the trigeminovascular system. Inflammatory neuropeptides, particularly CGRP, are involved, and other neurotransmitters are important, including serotonin, which helps explain some of the comorbid conditions such as anxiety and depression. Women may be more susceptible to migraines because estrogen increases NO levels. Once second- and third-order neurons are involved, central sensitization may occur with cutaneous allodynia and a diminished acute treatment response. Blood vessel changes occur but they are not the primary abnormality and are not time locked to the development of pain. Animal models suggest that drugs that prevent migraine seem to work at least in part by raising the threshold for the initiation of CSD.

USEFUL WEBSITES

International Headache Society
www.ihs-headache.org.

American Academy of Neurology
www.aan.com.

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