

Pathophysiology of Migraine

BY ROGER CADY, MD

THE PATHOPHYSIOLOGICAL UNDERSTANDING OF MIGRAINE has advanced considerably in the last two decades. Migraine has evolved from a vascular disorder to a complex neurological disorder. Additionally, the traditional view of migraine as being an episodic pain disorder is being supplanted by a disease model where migraine is considered a chronic disease with episodic manifestations. These changes have important implications to the diagnosis and management of the migraine patient. This article will review the evolution of these changes and their meaning in the care of the migraine patient.

Introduction

EPIDEMIOLOGICAL STUDIES SUGGEST that 12% of the adult population in the United States suffers with migraine. There is a significant gender bias for migraine with approximately three times as many women with migraine as men. In the general population this equates to 18% of adult women and 6% of adult men (1). Women also suffer a significantly greater burden with migraine in terms of both frequency and impact. In clinical populations, migraine is disproportionately represented relative to the general population, with an estimated 25% of women between the ages of 25 and 45 having migraine (2).

Historically, migraine has been considered a self-limited episodic pain syndrome. However, in the most recent revision of the headache classification system of the International Headache Society (IHS), migraine has been for the first time divided into an episodic and chronic form—with episodic migraine being considered a precursor to chronic migraine (3), implying that migraine can be progressive. Many other studies have demonstrated that, as migraine becomes chronic, it extracts a substantial toll from individual sufferers, their families, employers, and society in general. This suggests that migraine may be better understood as a chronic disease, with episodic manifestations that spans decades of an individual's life, and that a significant percentage of the migraine population will evolve into chronic migraine. Chronic migraine is associated with a pervasive neurological disturbance that includes chronic headache, mood disorders, sleep disturbances, and non-headache pain (4). This underscores the need for aggressive medical management of the patient with migraine.

Pathophysiological Models of Migraine

HAROLD WOLFF IS CREDITED as providing the first scientific support for the vascular theory of migraine (5). Based on laboratory studies with ergotamine, Wolff hypothesized that migraine was associated with an initial phase of vasoconstriction, followed by a compensatory phase of vasodilatation. The vasoconstriction was believed to be associated with oligemia, and the resulting reduction in cerebral blood flow could be severe enough to generate the event of aura. Vasoconstriction would be followed by an exaggerated compensatory vasodilatation, resulting in perivascular edema and inflammation, which in

turn lead to the headache of migraine. The theory was the dominant explanation of migraine for nearly 50 years.

However, several researchers and clinicians began to recognize inconsistencies with the vascular theory. Blau articulated the Phase Model of migraine (6) that included a prodrome phase which, while common clinically, was difficult to explain using the vascular model. Olesen, using cerebral Doppler blood flow studies, demonstrated that vasoconstriction did occur, but the timing of vasoconstriction did not precede the aura and continued well into the headache phase of the migraine (7). These two sentinel observations were instrumental in undermining the vascular etiology of migraine and opened the door for further explanation of the pathophysiology of migraine.

Evolution of a Modern Pathophysiological Model of Migraine

CONCOMITANT WITH THE WORK OF BLAU AND OLESEN, other researchers were studying the role of serotonin (5 HT) in the pathogenesis of migraine. Through painstaking efforts, serotonin agonists eventually emerged as a treatment for acute migraine. Humphrey developed sumatriptan (8), the first of a novel group of compounds called triptans which were highly selective agonists of the 5 HT-1 b/d serotonin receptors. Subsequent clinical studies demonstrated high efficacy of sumatriptan in the treatment of acute migraine. In an effort to understand the role of serotonin in migraine, scientific attention turned to the trigeminal vascular system. Serotonin agonists (sumatriptan) were determined to cause vasoconstriction of meningeal vessels and inhibit the release of various peptides from the trigeminal afferent, including calcitonin gene-related peptide (CGRP), neurokinins, and Substance P (9). In addition, the firing threshold for the trigeminal afferent was elevated. This provided a tidy mechanism to explain migraine and the efficacy of sumatriptan as a migraine treatment.

However, the trigeminovascular theory, as it became known, failed to explain specific migraine triggers such as menses, premonitory symptoms, the mild “nonvascular” headache phase of migraine, and neurological symptoms such as cognitive impairment that commonly occurred during migraine. These discrepancies led researchers to a neurogenic theory of migraine, which viewed the brain as the origin of migraine. According to this

theory the genetically sensitive migraine brain, when exposed to a migraine-inducing environment, would undergo neurochemical alterations resulting in premonitory symptoms. This alteration in neurochemical balance of the central nervous system could lead to trigeminovascular activation with the release of vasoactive peptides and neurogenic inflammation. This in turn lowered the sensory threshold for trigeminal input entering the brainstem at the Nucleus Claudalis of the Trigeminal Nerve. Sensory input from the C1 and C2 dermatomes would be integrated with the trigeminal input, and eventually synapse in the somatosensory and limbic cortex, where it is interpreted into conscious awareness as headache.

Later work by Hargreaves (10) and, later, Burstein (11), demonstrated sensory windup of peripheral sensory input in the brainstem and the evolution of central sensitization and eventually cutaneous allodynia. Thus, migraine can be thought of as occurring in a series of stages. The first of these is the interaction of the genetically prone migraine brain with events capable of provoking migraine. This clinically would be associated with the premonitory phase of migraine. The second would be alteration of central pain processing mechanisms. Clinically, this would be observed as the mild headache phase of migraine. The third stage would be trigeminovascular activation and peripheral sensitization. Clinically, this correlates with throbbing pain initiated by Valsalva or vascular distention. The fourth stage would be central sensitization, where second-order neurons are sensitized by the excess peripheral input from sensory neurons. The central neurons can sensitize higher order neurons until eventually migraine becomes an allodynic pain condition. Clinically, this would correlate with cutaneous allodynia.

Clinical Pathophysiology of Migraine

WOLFF DESCRIBED MIGRAINE as occurring in three phases: preheadache, headache, and postheadache. (5) However, it was Blau who first described the phase model of migraine and detailed the clinical evolution of an acute attack of migraine. In this model, migraine is hypothesized to evolve through five clinical phases: prodrome, aura, headache, resolution, and postdrome (6).



(opposite)

Title: Migraine - A Parade of Pain
Artist: Richard Benbrook

Migraine Masterpieces art used with permission of the National Headache Foundation.
For more information on headache causes and treatments visit www.headaches.org

Prodrome and the Premonitory Phase of Migraine

PREMONITORY SYMPTOMS consist of symptoms that occur prior to the onset of headache. They are distinguished from aura in that they are nonfocal and include symptoms such as fatigue, muscle pain in the neck or head, food cravings, cognitive impairment, nasal congestion, anxiety, and irritability. If they coalesce into a recognizable pattern from which the patient can predict the headache phase of migraine, they are often

postural changes such as forward bending. It is believed to reflect the time period from trigeminal activation through peripheral sensitization of the involved trigeminal afferents. Thus it can be minutes to hours in duration depending on attack and patient profile.

The moderate to severe phase of headache represents the development of central sensitization and, for a majority of migraine sufferers, the development of cutaneous allodynia.

Headache is characterized by a throbbing nature and the presence of associated symptoms such as nausea, photophobia, and phonophobia. The occurrence of cutaneous allodynia can be confined to the distribution of the trigeminal nerve or extracranial and reflects sensitization of central pain pathways. Clinically, Burstein et al (14) have demonstrated that intervention with triptans results in pain relief, but not resolution when the triptans are initiated during moderate to severe pain. This is in contradistinction to triptan intervention during mild pain, which is characterized by substantial pain-free outcomes within 2 hours (15,16,17). The headache phase of migraine typically lasts 4 to 72 hours.

Post Headache Phase of Migraine

THE MECHANISM BY WHICH THE NERVOUS SYSTEM RECOVERS spontaneously from an attack of migraine is unknown. However, clinically, headache resolution is most often associated with sleep. Following headache resolution, patients are often left with symptoms similar to those observed during the premonitory phase: fatigue, lethargy, irritability, cognitive dysfunction, and tender, sore muscles. This phase of migraine is called the postdrome, and can last up to 48 hours. Postdromes can add significantly to the overall disability of a migraine attack.

Convergence Hypothesis

THE CORRELATION OF THE CLINICAL PHASES of a migraine attack and pathophysiology of migraine with clinical diagnosis of primary headache disorders was first described by Cady et al and called the Convergence Hypothesis (18). In this model, the pathophysiology underlying a migraine attack can be terminated at any point in its evolution. If the migraine process is terminated after premonitory symptoms are observed, no specific diagnosis is typically possible. If the process terminates after aura, a diagnosis of migraine without aura is possible; if it is followed by a low-grade headache without associated symptoms, a diagnosis of aura with tension-type headache is made. Likewise if there is no aura but the migraine process terminates during the mild headache phase, a diagnosis of tension-type headache is made. If the headache phase progresses to include some headache and associated features of migraine, but

not enough to fulfill IHS criteria for migraine 1.1, the probable migraine is diagnosed; and, finally, if it progresses further and enough headache characteristics and associated symptoms occur to fulfill IHS criteria for migraine, then IHS migraine is diagnosed. Thus, the spectrum of headache from IHS tension-type headache to migraine is hypothesized to arise from a common pathophysiological mechanism rather than distinct pathophysiological mechanisms. This offers considerable utility for clinicians and their patients in terms of understanding the spectrum of symptoms occurring during migraine (Figure 1).

The Spectrum of Symptoms in Migraine

UNDERSTANDING MIGRAINE AS A NEUROLOGICAL PROCESS provides the clinician the ability to explain the wide array of symptoms commonly encountered during a migraine attack. For example, during the premonitory phase, migraine

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patients will note food cravings, fatigue, muscle tenderness (especially in the neck and head), nasal congestion, facial pressure, poor concentration, and changes in cognition. The inability to explain these symptoms utilizing peripheral models of migraine pathogenesis has, in part, been responsible for the popularity of such headache diagnoses as sinus headache, tension-migraine, mixed headache, and numerous other clinical descriptions of headaches with prominent nonvascular headache symptoms. The neurogenic model, on the other hand, can explain autonomic symptoms of nasal congestion, rhinorrhea, and facial pain as well as central derived symptoms such as fatigue and cognitive impairment. This model also permits understanding of muscle pain as central alterations of pain perception rather than peripheral causes of headache. Utilizing a central model for migraine can assist both patients and clinicians in avoiding the pitfall of erroneous diagnosis and treatment.

The Disease of Migraine

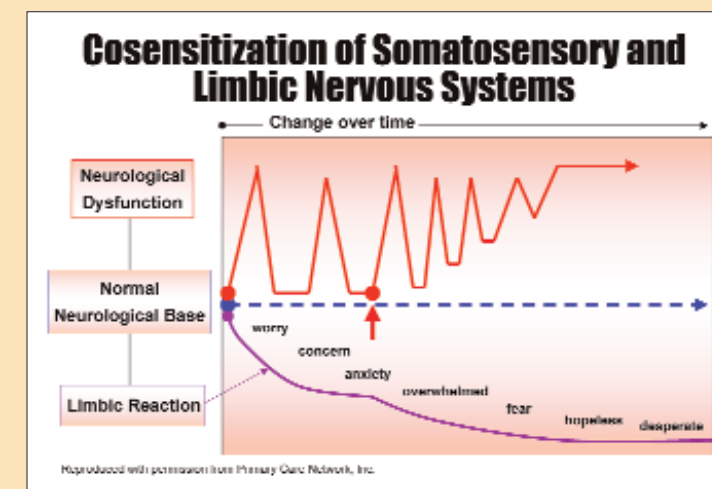
AS AN ATTACK, migraine is viewed as an episodic pain syndrome, with minimal or no consequences to the patient occurring between episodes of headache. However, considering that patients will experience repeated attacks of migraine at varying frequencies over decades of their lives, another picture of migraine often emerges. For the first time in the most recent classification system proposed by the IHS, a diagnosis of chronic migraine has been accepted, and chronic migraine is viewed as arising from episodic migraine.

Interestingly, in coming to this diagnosis, the IHS classification committee first proposed that chronic migraine was simply frequent attacks of acute migraine (>15 per month). However, given the IHS definition of medication-overuse headache, it became readily apparent that this diagnosis of chronic migraine

was inadequate. Thus, an appendix definition was proposed after the original publication, which used a definition of chronic migraine as consisting of at least eight attacks per month of IHS 1.1 migraine, or an attack of headache not fulfilling IHS migraine criteria but responding to a migraine-specific medication, and that seven attacks of headache per month could fulfill IHS criteria for tension-type headache. (19) In addition, the IHS recognizes that tension-type headache has a robust response to triptan in patients with migraine. This diagnostic scheme is a major departure of the taxonomy of the IHS where each individual headache is diagnosed independently and clears the way for understanding the pattern and impact of primary headaches in patients.

This supports earlier models of migraine proposed by Raskin (20) and Mathew (21) of frequent episodes of migraine transforming to chronic migraine. In these models, the neuro-

logical baseline between headaches changes, and patients fail to return to normal neurological function between episodes of migraine. Clinically, this is often seen as the emergence of chronic daily tension-type headache, or the occurrence of psychological diseases such as anxiety or depression. This association has been referred to as co-morbidity, implying a higher than expected statistical association between two disorders. However, more recently it has been proposed that these associated diseases are etiologically connected, and that there is a sensitization of the nervous system that occurs with frequent bouts of these related disorders that physiologically predisposes a patient to their occurrence. This is called co-sensitization and lends itself to a model of migraine as a chronic disease with episodic manifestations, capable of progressing into a chronic disease state (22). Thus, migraine progression is considered in a similar manner to the way asthma is viewed, with the potential to become chronic obstructive pulmonary disease. Considering migraine in this manner has considerable implications to its treatment and management.



Conclusions

THE PATHOPHYSIOLOGY OF MIGRAINE has advanced considerably over the last 20 years. Attacks of migraine are considered to originate in the brain, thus making migraine a neurological rather than vascular disease. In addition, frequent episodes of migraine can lead to chronic migraine, which is a complex disorder that is characterized by the near daily occurrence of low-grade headache, frequent attacks of IHS migraine, and prolonged neurological disruption, such as depression, anxiety, and myofascial pain occurring concomitantly with chronic headache. This has led to migraine being considered a chronic, genetically determined disease with episodic manifestations that can, over time, progress into a chronic disease state.

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