Advances in the Basic and Clinical Science of Migraine

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Migraine continues to be an elephant in the room of medicine: massively common and a heavy burden on patients and their healthcare providers, yet the recipient of relatively little attention for research, education, and clinical resources. Its visibility is gradually increasing, however, as advances in genetics, imaging, epidemiology, and pharmacology produce a more definitive understanding of the condition, and identify more specific and effective treatments. Rapid evolution of concepts regarding its prevalence, pathophysiology, and clinical management is leading to growing recognition of migraine as a fundamentally important disorder of the nervous system.

Ann Neurol 2009;65:491–498

The quantification of migraine occurrence in recent population studies confirms that it is extraordinarily common. The American Migraine Prevalence and Prevention Study indicates that the cumulative lifetime incidence of migraine in this population is 43% for women and 18% for men.[1] Given that the diagnostic criteria are relatively stringent, the incidence may, indeed, be even greater. This means that nearly half of all women will experience migraine at some point in their lives. The remarkably common occurrence of migraine suggests that it may involve relatively minor perturbations of normal brain function and may, therefore, have much to teach us about the basic physiology of the nervous system.

A migraine attack is a spectacularly complex brain event that can produce a wide array of neurological and systemic symptoms. Although headache is typically its most prominent feature, a migraine may include multiple other symptoms that occur before, during, or after the pain. The second edition of the International Classification of Headache Disorders[2] has acknowledged more of these symptoms through an expanded classification of migraine aura to include sensory and language dysfunction, in addition to the classic visual aura. Other symptoms including mood change, fatigue, yawning, neck stiffness, polyuria, gastrointestinal disturbance, and a variety of visual, somatic sensory, and cognitive phenomena are among the clinical features that may precede, accompany, or follow the headache.[3–5] Electronic diary studies indicate that based on "premonitory" symptoms, patients are able to accurately predict the occurrence of a migraine up to days before it begins.[5] The pathophysiological processes underlying a migraine may therefore be occurring well before the headache, raising questions about how a migraine "attack" should be most accurately defined. The characterization of a migraine attack is further complicated by the considerable variability in clinical symptoms from one individual to the next, and from attack to attack within a given individual. What is clear, however, is that migraine involves multifaceted molecular, cellular, neuroanatomic, and neurochemical mechanisms.

Migraine Pathogenesis

There has been further movement away from the concept of migraine as a primarily vascular disorder. The hypothesis that migraine pain is caused by vasodilation, an idea that took hold with the work of Ray and Wolff[7] and Penfield[6] in the 1930s and 1940s, has been challenged by a variety of recent findings. Although intracranial vasodilation is an appealingly simple explanation for migraine pain, this hypothesis has never been capable of explaining the wide range of symptoms that may precede, accompany, or follow the pain. Multiple imaging studies have now confirmed that vasodilation is not required for migraine headache. Xenon blood flow studies, single-photon emission computed tomography, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) studies

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Potential conflict of interest: AGA Medical - Advisory Board, Medtronic - Advisory Board, Merck - Advisory Board and Speaker's Bureau, Minster Pharmaceutical - Research Grant Support.

Received Jan 13, 2009, and in revised form Feb 12. Accepted for publication Feb 27, 2009.

Published in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21691

show significant cortical hypoperfusion, in some cases followed by sustained hyperperfusion during a migraine attack. Olesen and colleagues[8] point out in their extensive earlier studies that headache typically begins during the cortical hypoperfusion phase and may end before the hyperperfusion resolves. The PET study of a patient with migraine reported by Woods and coauthors[9] provide a dramatic visualization of propagated hypoperfusion *during the pain phase* of a migraine attack, and Denuelle and colleagues'[10] recent series of migraine patients investigated with PET also demonstrated cortical hypoperfusion during the pain phase of migraine. These findings are not consistent with vasodilation as a primary trigger for pain and, to the contrary, suggest that headache may be triggered by hypoperfusion.

The migraine-inducing effect of vasodilating medications such as nitroglycerin and phosphodiesterase inhibitors has been used as argument for dilation of cerebral blood vessels as a cause of migraine pain. However, this argument has also been directly challenged by recent imaging studies, which demonstrate that migraine headache evoked by these medications begins well after the caliber of cerebral vessels has recovered to their baseline levels.[11,12] Similarly, some agents known to induce cerebral vasodilation, such as vasoactive intestinal peptide, do not evoke headache.[13] These studies provide further evidence that vasodilation is neither necessary nor sufficient for migraine headache.

Another corollary of the vascular hypothesis of migraine has been the concept that vasoconstriction is a primary mechanism by which caffeine, ergotamines, and triptans exert their therapeutic effect. But transcranial Doppler studies do not support this assumption,[14] and there is a growing understanding that each of these agents likely acts via alternative mechanisms. For example, increasing evidence indicates that the triptans may work at multiple sites along the trigeminal nociceptive pathway. Triptans inhibit nociceptive signaling not only at peripheral trigeminal afferents[15] but also in the trigeminal nucleus caudalis, in the periaqueductal grey, and in the thalamus.[16–18] Indeed, Goadsby[19] and colleagues, among others, have suggested that the efficacy of the triptans for migraine could be because of their duplicative actions at these different locations. Multiple migraine preventive medications including amitriptyline, divalproate sodium, and topiramate do not appear to have any primary effect on the vasculature. It is now clear that modulation of vascular tone is not a necessary mechanism for acute or preventive migraine therapy.

Migraine Genetics

Recent concepts of migraine pathogenesis have expanded their focus to include the changes in brain activity that occur before, during, and after the vascular phenomena. Migraine is currently viewed as an episodic disorder of brain excitability, akin to epilepsy and episodic movement disorders. The identification of multiple genes responsible for familial hemiplegic migraine (FHM) has provided strong support for this view. Characterization of the functional consequences of the mutations of the three different genes responsible for FHM indicates that each is capable of changing cellular function to increase brain excitability. In FHM type 1, calcium channel gene mutations can result in a gain of function that increases excitatory neurotransmitter release.[20] In FHM2, alterations in the Na^+/K^+ ATPase gene can reduce function of the enzyme, leading to an increase in extracellular potassium, thereby increasing neuronal excitability.[21,22] In FHM3, Na^+ channel gene mutations may change the kinetics of the channel such that action potentials can fire with increased frequency.[23] Although evidence from in vitro expression studies indicates that the effects of FHM mutations may be much more heterogeneous and complex than as simply characterized above,[22,24,25] it is clear that multiple distinct alterations in cellular excitability are capable of generating a final common phenotype of FHM. Other mutations of the same genes may result in seizures or ataxia, indicating that FHM may be considered part of an overlapping spectrum of episodic disorders of the central nervous system.[26] The genes responsible for more common forms of migraine have thus far been elusive. This may be in part because common forms of migraine may be caused by the combined effects of multiple genes and epigenetic factors, in contrast with the monogenic FHM syndromes.[27] There has been speculation that, like FHM, common migraine may also involve differences in genes involved in ion transport. However, a recent extensive screen of a European population concluded that common variants in ion transport genes do not play a major role in susceptibility to common migraine.[28] The search for genes for common migraine continues.[27]

Migraine Physiology and Anatomy

How do changes in cellular excitability trigger a migraine attack? One potential mechanism is by triggering waves of altered brain function such as cortical spreading depression (CSD), the slowly propagated wave of depolarization followed by inhibition of brain activity that Leao[29] first described in 1944. Since its original description, it has been hypothesized that the phenomenon of CSD is responsible for the migraine aura. PET and fMRI studies have demonstrated propagated waves of blood flow and brain activity during migraine attacks with temporal and spatial characteristics that are remarkably similar to those of CSD.[9,30,31] There is growing evidence that CSD in rodents represents a useful model with direct relevance to migraine

in humans. Genetic and sex-related factors associated with migraine in humans result in increased CSD in mice. Transgenic mice expressing CACNA1A mutations responsible for human FHM show a reduced threshold for the activation of CSD, more rapid propagation of CSD, and more pronounced motor deficits associated with CSD.[20,32] Also, female mice show a reduced threshold for CSD as compared with male mice, a finding that may be relevant to the 3:1 female/male prevalence of migraine.[33] Eikermann-Haerter and researchers'[32] recent studies suggest that ovarian hormones are responsible for the increased propensity to CSD in female mice. Conversely, Ayata and colleagues[34] performed important studies showing that CSD in rats is suppressed by multiple migraine preventive therapies with diverse pharmacological actions. CSD in rodents may therefore be a model that provides a platform for the investigation of established and novel migraine therapies.

It is important to recognize, however, that the propagated changes in cortical activity in migraine patients may not be the same as CSD in animal models. Although the classic electroencephalographic changes of CSD have now been observed in patients with brain trauma, subarachnoid hemorrhage, and ischemic stroke,[35,36] these changes have not been seen in migraine patients. This may be because surface electroencephalographic recordings have not been able to capture the direct current potential (DC) changes or the amplitude reduction ("depression") of electroencephalographic signal for which CSD was originally named. Magnetoencephalography may be a more sensitive approach to capture CSD in migraine patients[37] however it is also difficult to explain how an event such as classic CSD that is associated with such profound alteration of neuronal function could occur in the absence of more profound neurological impairment. One potential explanation is that laminar restriction of CSD allows it to be clinically silent. Another possibility is that slowly propagated changes in glial or vascular activity could extend well beyond a localized CSD event, or even occur in the absence of CSD. Astrocytes show intercellular waves of increased intracellular calcium concentration that can travel over long distances, and can modulate both neuronal and vascular activity.[38,39] These astrocyte calcium waves propagate with temporal and spatial characteristics that are remarkably similar to those of CSD, and, in fact, accompany CSD both in vitro and in vivo.[40,41] Chuquet and coauthors'[41] studies indicate that astrocyte signaling is responsible for cerebral vasoconstriction associated with CSD. Cerebral blood vessels may also have intrinsic mechanisms for propagated changes in caliber that are triggered by a localized brain activation.[42] Propagated changes in cortical activity that are predominantly glial and vascular (rather than neuronal) are therefore a speculative mechanism for the dramatic changes in blood flow and metabolism on PET or fMRI in migraine patients in the absence of corresponding neurological symptoms. Patients with more extensive neurological dysfunction, such as those with more pronounced aura or hemiplegic migraine, may have more significant neuronal dysfunction as is observed with classic CSD.

In addition to the acute changes in cortical activity during a migraine attack, clinical electrophysiological techniques provide evidence for interictal differences in cortical excitability in migraine patients. Characteristics of evoked potentials and responses to transcranial magnetic stimulation consistent with increased cortical excitability (or decreased inhibition) in patients with migraine have been reported by multiple investigators.[43–46] Others, however, find either no differences in clinical electrophysiological parameters or, in fact, changes in the opposite direction consistent with a reduced cortical excitability in migraine patients.[47] One explanation for these discrepancies is that the level of cortical excitability in migraine patients may be more variable than in control subjects, a concept that is supported by some transcranial magnetic stimulation studies.[48] Thus, rather than simply increased or reduced excitability, a dysregulation of cortical function leading to excessive swings in either direction[47,49] may predispose to migraine.

Evidence for changes in the function of the brainstem and hypothalamus in migraine also continues to accumulate. Premonitory symptoms, nausea, vertigo, and autonomic symptoms are among the clinical features of migraine that can be attributed to the brainstem and hypothalamus. Recent PET studies have confirmed the consistent activation of the pons and midbrain during a migraine attack,[50–52] and indicate that the laterality of pontine activation corresponds with the laterality of pain.[51] Other PET studies by Aurora and colleagues[53] have added to existing evidence suggesting that the metabolism and function in the brainstem may also be chronically altered in patients with chronic migraine.[54] In addition to brainstem activation, hypothalamic activation has now been visualized during a migraine attack.[52] There is increasing interest in the hypothalamic orexinergic system as a potential mediator of both migraine and cluster headache.[55,56]

The typical occurrence of the aura before headache supports the hypothesis that cortical activation leads to brainstem activation during a migraine attack. Consistent with this concept, studies in experimental models demonstrate that it is possible for CSD to activate neurons in the trigeminal nucleus caudalis via trigeminal afferents.[57] Conversely, it has been shown that stimulation of the locus ceruleus can evoke reductions in cerebral blood flow, raising the possibility that a process beginning in the brainstem could generate cortical hypoperfusion associated with migraine attacks.[58] But it

is also possible that a migraine attack is a generalized brain "state," wherein multiple brain regions are activated independently or in parallel, without the requirement for any orderly anatomic progression. This concept may explain the remarkable clinical heterogeneity of migraine.

A Disorder of Sensory Function

A principal outcome of the anatomic and physiological processes underlying migraine is a derangement of sensory function. In addition to experiencing pain, migraine patients are sensitive to light, sound, smell, and touch during an attack. There has recently been an increased effort to quantitatively characterize these sensory changes. A number of studies have focused on allodynia, the perception of normally innocuous stimulation of the skin as uncomfortable. Quantitative sensory testing and questionnaire-based studies indicate that a majority of patients experience allodynia during a migraine attack, and that the severity of allodynia is correlated with migraine duration, attack frequency, and disability.[59–62] Burstein and colleagues[60] reported that allodynia develops gradually during a migraine attack, and that its occurrence is correlated with reduced responsiveness to triptan therapy. They hypothesized that allodynia is a symptom of progression of a migraine attack to a state of central sensitization that is refractory to triptans. This hypothesis has been challenged by other studies that found that the presence of allodynia did not predict responsiveness to triptans.[63,64] Much of the thinking about allodynia in migraine has paralleled paradigms of allodynia in neuropathic pain, wherein it is a secondary response of the central nervous system to nociceptive input from the periphery.[65] In migraine, however, patients commonly have central nervous system activation before the onset of pain (as evidenced by clinical symptoms and functional imaging). Central sensitization in migraine could therefore occur primarily from the direct activation of the cortex, thalamus, and brainstem, rather than secondarily as a consequence of a peripheral activation. Consistent with this concept, Sand and investigators[66] recently reported that thermal pain thresholds were reduced in migraine patients well before the onset of headache. Cutaneous allodynia may therefore represent a primary dysregulation of central sensory processing similar to that which is responsible for the increased sensitivity to light, sound, and smell. Its potential utility as a migraine marker and guide to therapeutic decisions is a topic of ongoing studies.

Progression of Migraine

For many patients, migraine is an infrequent occurrence that can be effectively managed with current therapies, but for many others, it progresses to a frequent, chronic condition that is refractory to standard management. These unfortunate individuals with frequent or daily migraine represent the majority of patients seen in headache specialty clinics, and there is a growing recognition that chronic migraine represents a distinct entity that may have distinct pathophysiology. This recognition is reflected by the second edition of the International Classification of Headache Disorders designation of chronic migraine as a specific diagnosis.[2] Information is beginning to accumulate regarding the process by which migraine is "transformed" from an episodic to a chronic problem. It is now widely accepted that, in some patients, the frequent use of analgesic medications may play an important role in this process. The second edition of the International Classification of Headache Disorders designations for headache associated with medication overuse are rapidly evolving.[67,68] Bigal and Lipton's[69] recent studies indicate that migraine progression associated with medication use may have a specific pharmacology. Their population study found that the use of opioids and barbiturates (ie, butalbital) are associated with the development of chronic migraine, whereas triptan use was not, and nonsteroidal use appeared, in fact, to be protective. Their findings also suggest that there is a duration of opioid use (8 days or more per month) that is associated with a substantially greater risk for development of chronic migraine. Progression of migraine in response to opioids could involve mechanisms similar to those that are responsible for opioid-induced hyperalgesia, the paradoxical sensitization to nociceptive stimuli that results in increased pain in some patients receiving opioid analgesics.[70] Although there is a growing consensus that chronic opioids or butalbital, or both, are not advisable for migraine patients,[71] at this stage, there are still no guidelines regarding the questions of whether specific medications, or frequency or durations of their use, should be avoided to reduce risk for migraine progression.

Patent Foramen Ovale and White Matter Lesions

There has been considerable recent interest in the correlation between patent foramen ovale (PFO) and migraine. Multiple investigators have reported an increased prevalence of PFO in patients with migraine with aura, and several uncontrolled studies indicated significant improvement in migraine frequency PFO closure (see Schwedt and coauthors'[72] review). It has been suggested that microemboli or other factors crossing from the right-to-left circulation could act as a migraine trigger, possibly by evoking CSD. However, there has yet to be any high-quality evidence for the efficacy of PFO closure as preventive therapy for migraine.[72] The first controlled study to investigate this question did not reach a positive end point and was associated with substantial controversy.[73] Other studies examining the efficacy of PFO closure for prevention

of migraine are under way; these may shed further light on this potential migraine mechanism.

Another topic of recent attention has been white matter lesions visualized with MRI. It is now well established that some patients with migraine have diffuse, small foci of subcortical hyperintensity on T2 and flare sequences[74,75] that are clinically silent. The cause of these lesions and their functional significance remain uncertain. One hypothesis is that they are ischemic lesions, possibly a result of the cerebral oligemia that has been observed with functional imaging studies of migraine patients. Another hypothesis is that these lesions could be the consequence of microemboli traveling through a PFO. However, multiple studies have now documented no increase in the number of white matter lesions in patients with migraine with aura associated with right-to-left circulatory shunt as assessed by transcranial Doppler.[76,77] And at least one report indicates that the lesions may be transient, a finding that is not consistent with an ischemic causative factor.[78] Another potential explanation may be that they represent areas of focal breakdown of the blood–brain barrier (BBB). Pathological analysis of unexplained MRI white matter lesions has implicated BBB breakdown as a cause.[79] Although the function of the BBB in migraine is controversial,[80] the observation that CSD in animal models is associated increased permeability of the BBB[81] raises the possibility that focal breakdown of the BBB could be a mechanism for MRI lesions in migraine. Longitudinal studies that follow these MRI lesions and evaluate for their potential functional consequences over time will be of great interest.

Advances in Migraine Therapy

More than 15 years after the introduction of sumatriptan, triptans continue to be a mainstay of acute migraine therapy. Although there was initially significant concern regarding their potential for serious adverse vascular effects, the small incidence of such adverse effects over 15 years of extensive worldwide use indicates that they are generally quite safe.[82] Multiple European countries have acknowledged the safety of the triptans by allowing them to be dispensed by pharmacies without a physician's prescription. Although they have had a dramatic positive effect on the lives of many patients, there are many others for whom triptan therapy is either only partially effective or not at all. For some, triptans can be highly effective in relieving pain and nausea, and yet relatively ineffective at reducing other migraine symptoms. The need for alternative acute therapies, as well as more effective preventive therapies, remains substantial.

In addition to different preparations or delivery methods for triptans or ergotamines, drugs targeting glutamate, nitric oxide, and calcitonin gene-related peptide (CGRP) signaling are among those in development as acute therapy for migraine. Of these, CGRP receptor antagonists may be the closest to availability for widespread clinical use. Interest in the use of CGRP antagonists for migraine began with the observations that CGRP is released during a migraine attack,[83] and that infusion of CGRP can induce a migraine.[84] Initial studies with intravenous administration of a CGRP antagonist found that it was effective as abortive therapy.[85] The development of oral CGRP antagonists has taken several years, but recent clinical trials indicate that a CGRP antagonist (telcagepant) in tablet form is an effective acute therapy for migraine and is well tolerated.[86,87] These initial studies suggest that CGRP antagonists may be an important option for acute migraine therapy.

There has also been significant progress in the preventive therapy for migraine. Evidence for the efficacy of topiramate as preventive therapy has continued to accumulate over the last several years, with recent studies indicating efficacy for chronic migraine.[88,89] An interesting issue about topiramate (and other preventive agents) is the optimal duration of therapy. One recent study concluded that benefit from preventive therapy with topiramate was sustained after cessation of the medication after 6 months of use.[90] These results raise the possibility that sporadic rather than continuous long-term use of preventive migraine therapy may be optimal for some migraine patients. Despite the availability of a variety of preventive agents with proven efficacy, however, the practices of neurologists worldwide continue to be filled with patients with chronic migraine for whom currently available preventive therapies are either ineffective or poorly tolerated. As mentioned earlier, CSD in animal models may represent a platform for discovery of new preventive therapies.[34] Tonabersat is an example of a CSD inhibitor that is in clinical trials for prevention of migraine.[91] Memantine, an activity-dependent *N*-methylD-aspartate receptor blocker, is another example of a potential therapeutic compound that has been shown to inhibit CSD.[91] Because it is already in approved clinical use for the treatment of Alzheimer's disease, it has been available for off-label use for migraine prevention. Encouraging results of early observational studies suggest that memantine is a good candidate for formal clinical trials. Other novel potential therapeutic approaches involve different forms of neurostimulation; transcranial magnetic stimulation and occipital nerve stimulation are among those being studied as potential acute and preventive migraine therapies. Because it is likely that diverse genetic and neurochemical mechanisms underlie migraine in different individuals, it may be difficult to find a single approach that broadly targets all of these mechanisms. The identification of new migraine genes and specific clinical biomarkers may lead to treatments that are tailored to distinct therapeutic targets in individual patients.

The horizons for migraine research and treatment continue to expand, with broader views of pathophysiology and potential therapies driven by advances in basic and clinical science. These are exciting times for the field of headache medicine and should be hopeful times for the many millions of individuals worldwide who suffer from this disabling disorder.

This work was supported by a grant from the NIH (National Institute on Drug Abuse, P50DA-05010) and the Migraine Research Foundation.

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