Neurology® Clinical Practice

Taking the headache out of migraine

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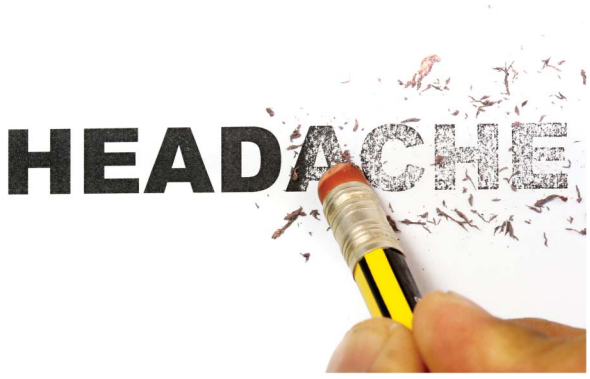
Summary

Migraine is a disease that contributes to major disability. Perhaps because migraine attacks are not immediately life-threatening per se and individuals return to a "normal" state between attacks, it is not taken seriously. However, migraine is associated with a number of comorbidities, including psychiatric disease, stroke, and other chronic pain disorders. Current acute treatments for episodic migraine are relatively effective, but preventive treatments for episodic and chronic migraine are far less so. Recent functional imaging studies have shown that the disease affects brain function and structure (either as a result of its genetic predisposition or as a result of repeated attacks). The current evidence in the pain field is that changes observed in brain function and structure may be reversible, adding credence to the notion that treating the disease aggressively and early may be beneficial to patients. Here we suggest a change in our approach to a disease that is currently not treated with the urgency that it deserves given its global prevalence, disease burden, and effects on brain function.



Migraine is considered by the World Health Organization to be the third most prevalent and the seventh most disabling illness in the world.[1,2] Migraine accounts for approximately 20% of the International Classification of Functional Disability and Health.[3,4] In the United States, migraine affects more than 36 million adults. For most, the disease affects them during the most formative and productive periods of their lives (ages 20–50 years); furthermore, 6%–10% of school-aged children (ages 5–18 years) experience migraine at a time of important social and cognitive development.[5,6] The cost to society in the United States alone exceeds $20 billion annually.[7] In approximately 2% of the population, migraine progresses to a more disabling form—chronic migraine—in which patients experience symptoms on a daily or near-daily basis.[8,9] The lifetime prevalence of migraine is 19%.[10] Despite the burden associated with migraine, it remains stigmatized, underestimated as a major clinical problem, underdiagnosed, and undertreated.[11,12] Suboptimal treatment has been demonstrated to be a risk factor for

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> *For I had no brain tumor, no eye strain, no high blood pressure, nothing wrong with me at all. I simply had migraine headaches, and migraine headaches were, as everyone who did not have them knew, imaginary.*
>
> *Joan Didion*

progression to chronic migraine, which is associated with significantly greater disability, decreased health-related quality of life (HRQoL),[4] greater comorbid disease, and higher cost compared with episodic migraine.[13] Even when it is accurately diagnosed, health care professionals may not identify the levels and dimensions of functional impairment imposed by migraine.[14,15]

Migraine is not immediately life-threatening, there is generally no objective physical disability, and the person may appear well between attacks. Migraine is comorbid with psychiatric disorders (e.g., depression and anxiety[16]), cardiovascular disease (e.g., angina and myocardial infarction[17]), metabolic syndromes (e.g., obesity[18]), other neurologic disorders (e.g., epilepsy[19] and sleep disorders[20]), and gastrointestinal disorders (e.g., irritable bowel syndrome[21]) and lacks a specific disease biomarker. The comorbid psychiatric disorders and the frequent association with emotional stress as a trigger of attacks contribute to the stigma and the misconception that migraine is a benign psychosomatic disorder. As a consequence, migraine has remained in the shadows of medicine and neurology. In a recent study, migraine was shown to be a leading cause of suicide in veteran[22] and civilian populations,[21,23] and suicide may be more frequent in patients with aura.[24] Migraine places a major burden on the lives of these individuals in terms of functional impairment[4] and diminished HRQoL between attacks.[25] This interictal burden of migraine has become increasingly recognized as a source of significant functional impairment, with physical, emotional, economic, and social ramifications.[26,27] While some of this interictal burden is associated with the unpredictability of attacks and the inability to plan or accept responsibilities, it is also a sign of the chronic functional and structural changes in the brain that may be both an intrinsic feature of the migrainous brain and a consequence of repeated attacks over time and the drugs used to treat attacks.[28–30]

Treatment options: Renewed efforts to get out of the abyss

The medical and research communities have not treated migraine with the level of urgency that it deserves given its global prevalence, disease burden, and effects on brain function. Its unrecognized status as a brain disease needs to change. Only one class of medication has been designed and approved to treat acute attacks, and no preventive therapy has ever been specifically designed or approved to prevent attacks. This is largely because of the relative dearth of funding dedicated to migraine research, which is due at least in part to the fairly recent emergence of headache medicine as a legitimate clinical and scientific career pursuit.

An analysis of annual NIH research funding relative to disease-specific burdens (disability-adjusted life years) predicted migraine funding levels similar to schizophrenia and cirrhosis.[31] In 2012, the NIH funded $266 million for schizophrenia, $288 million for cirrhosis, and $18 million for migraine. There has been only one migraine "Request for Applications" in NIH history. While there has been an increase in migraine funding in recent years, those of us in the field must lobby for more research and educate our colleagues in the scientific arena regarding migraine as a disease with an important unmet need. In an earlier evaluation of

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chronic diseases that affect the American population, including migraine, the authors demonstrated a "persistent finding that nonfatal conditions do not receive health services care commensurate with their prevalence."[32]

Fortunately, the tremendous efforts of creative and industrious academic clinicians and scientists working on shoestring budgets have begun to unravel the fundamental mechanisms of migraine, the chronic functional and structural changes within the brain that occur over time, and the high-value therapeutic targets against which novel disease-specific drugs have been developed.

Calcitonin gene-related peptide (CGRP) is the most promising and validated of those targets. CGRP is found throughout the trigeminovascular system as well as in central brain regions considered important in migraine pathogenesis.[33,34] Its role in migraine has been underscored by a number of experimental and clinical observations: during spontaneous migraine attacks, there is an increase in CGRP within venous blood and saliva[35,36]; IV infusion of recombinant human CGRP can trigger a migraine attack[37]; and elevated CGRP serum levels can be reversed with triptan administration.[38] In addition, small molecule CGRP-receptor antagonists have demonstrated efficacy in treating acute migraine headache in double-blind, randomized, placebo-controlled trials,[39–42] and monoclonal antibodies against the CGRP molecule and its receptor have been developed and positive phase 2 prevention studies have recently been reported.[43–45]

Fundamental insights: Repeated "brain attacks" may disrupt brain function and structure

Brain imaging has revolutionized our insights into a number of CNS diseases. Migraine is no exception. Brain imaging has contributed to the notion that migraine is a disease that affects the brain.[46] Work from laboratories across the United States, Europe, and Asia is defining alterations in brain function that were previously unimagined. These are reviewed in detail elsewhere but examples of recent findings are summarized as follows:

1. Changes in brain function and structure occur with migraine. The more migraine attacks per month, the more significant changes in gray matter volume in cortical and subcortical regions.[47] These regions include cortical regions such as the somatosensory region[48] and the insula[49] and subcortical regions such as the basal ganglia[50] and hippocampus.[51] Female migraineurs have greater changes in gray matter in some brain areas (e.g., precuneus and insula) than male migraineurs, and there are significant differences in responses to sensory stimuli (e.g. heat)[49] and functional changes of altered connectivity.[52]
2. Alterations in descending pain modulation are also inferred from brain imaging,[53,54] suggesting that in migraine, like in many chronic pain diseases, ascending nociception is facilitated by diminished inhibitory (or increased facilitory) systems. It is thought that these begin to functionally fail as migraine undergoes chronification.
3. The brain is considered to be hyperexcitable in those with migraine, notably in cortical regions. Early insights into brain neurochemistry using magnetic resonance spectroscopy confirm increases in excitatory amino acids.
4. Alterations in white matter integrity in the interictal state.[55]

5. The variety of symptoms that constitute the premonitory (preheadache) phase of migraine have been recently demonstrated to have their own location-specific imaging signature highlighting the CNS origin of the attack.[56]
6. Dynamic alterations in brain function are supported by gray matter changes in chronic migraine that reportedly reverse with medication withdrawal.[57]

Other views on how imaging has contributed to brain changes are noted elsewhere.[58] Taken together, the insights implicate a dynamic plasticity of the migraine brain. Initial reports on reversal of gray matter changes in chronic migraine with opioid withdrawal suggest that targeting the stability of the brain in migraine is critical. Indeed, allostatic load in migraine is a problem, and diminishing this load (stress) may be one opportunity to normalize or help stabilize brain dysfunction in migraine.[28] Instead of a normal and adaptive recovery from an acute stressor, allostatic load is defined as the cumulative and potentially damaging effects of chronic or repeated stressors that may contribute to disease worsening.[28,59,60] While there is little doubt that changes are present in the brains of patients with migraine, clinical translation with regard to imaging biomarkers for progression, treatment response, and endophenotypes is not available and will require a large longitudinal collaborative international effort that involves the systematic study of carefully phenotyped patients with standardized brain imaging.

Neurobiology breakthroughs: Putting migraine ahead

Scientific breakthroughs have contributed to a better understanding of the neurobiology of migraine, sometimes with direct clinical implications. The insights garnered from preclinical work have provided new insights into the brain mechanisms involved in migraine. Examples include (1) definition of new genetic susceptibility loci in patients[61]; (2) discovery of alterations in ion channels and an association with sleep-related genes[62]; and (3) definition of neural pathways providing a mechanism for photophobia in migraine.[63] These are just 3 examples from a rapidly explosive field of new insights into the disease.

Imaging promises to deliver a method for differentiation of subgroups of migraineurs who may be responders and nonresponders to medication, predict chronification, and provide objective measures for early brain changes in treatments. It provides a noninvasive approach to defining psychophysical, pharmacologic, and temporal measures on the disease state and treatment effects.[64]

Headache pain: The tip of the iceberg

Migraine is a CNS disease with multiple manifestations and a complex and not completely understood pathophysiology. The headache represents the painful phase of an underlying process that has been difficult to measure. The clinical manifestations, which include a wide range of symptoms and signs including pain, cognitive dysfunction, sensory hypersensitivity (light, touch, odor, sound), emotional and affective symptoms, nausea, emesis, vertigo, and focal neurologic symptoms and signs, reflect and correlate with focal dysfunction in brain regions that are anatomically specific.[65] In pain neurobiology, activation of pain fibers is well known to produce changes in the nervous system that range from morphologic to chemical and functional alterations in sensory processing.[66–68] Recently, such changes have also been demonstrated in migraine models and clinical studies in patients with migraine. Some examples of how migraine affects the nervous system include the following:

1. Acute migraine attacks alter brain processing. There are obvious changes, such as hemiplegic migraine and Alice in Wonderland syndrome, but it is the repetitive and more subtle changes that may manifest as autonomic changes, and increased sensitivity to light, sound, and smell.
2. The interictal migraine state is not a "normal brain state." There are now abundant data to support increased functional connectivity and hyperexcitability of brain networks involved

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in processing nociception, sound, light, and emotions in between "attacks" or when pain is not present.

3. Increased migraine frequency leads to altered brain processing. The most easily clinically recognized symptom is allodynia, a manifestation of central sensitization that is more common in chronic migraine.

Taken together, these tangible consequences of migraine – whether due to migraine itself or comorbid disease – reflect a highly dysfunctional state. We currently do not know the long-term effects of migraine. Is it possible for the brain to recover and revert to a normal brain state? Does the brain adapt once an individual's migraine attacks are considerably fewer or remit altogether? Does preventive therapy alter the long-term prognosis or reduce the frequency of comorbid disease (e.g. stroke)? Longitudinal studies are needed to answer these questions.

In most patients it is likely that, aside from the headaches themselves, there are multiple drivers that modulate brain systems. It is important to recognize these not as single contributors but as possible enhancers that add to the flow of the pathophysiologic stressors on the brain. The concept of allostatic load, discussed above, is aptly applied to the migraine brain. A consequence is the abnormal response of the brain to environmental, physiologic, and biological processes.

Viewing migraine a brain disease: Changing attitudes and medical practice

Translating insights from research into clinical practice is usually not an easy task. It takes a huge effort in terms of education to clarify the benefits to patients and health care professionals. Adoption of the idea that we should inform patients that "migraine alters your brain" has its challenges. Focusing on the symptoms of the ictal phase (pain, nausea, vomiting, photophobia, etc.) in educating patients about migraine is obviously important. It is also clear that like many other chronic diseases (e.g. asthma, diabetes, hypertension), there is a spectrum of illness. Some patients have mild intermittent and self-limited disease in whom symptoms remit, while others have a chronic progressive course with disabling illness. It appears clear that the functional and structural brain alterations are more likely and demonstrable in those with more chronic and progressive disease. However, getting patients to understand that their disease alters the brain functionally and structurally over time is important. Such an understanding may have enormous effects on patients' and the general public's attitude toward the disease, the need for a disease state model of care, patient compliance with treatment regimens, and the mobilization of funding and educational resources to advance the science and the ability of health care providers to manage this common disease.

A new imperative: Reconstructing our clinical view

Migraine has genetic, environmental, and likely epigenetic causes. No matter what the etiology, if we accept that migraine is a disease of the brain, we transform our current clinical construct about the disease and treatment approaches to patients. Patients would understand the importance of the full spectrum of treatments, pharmacologic and behavioral, as well as lifestyle modifications. Telling patients that they have a neurologic disorder will enhance a therapeutic alliance, help focus our approach to research and drug development, and further increase

our understanding of how treatments effect, modulate, or alter brain function in the context of both symptom management and disease modification. Within the foreseeable future, we believe that brain measures of function and structure will begin to make their way into routine clinical practice. These measures will provide objective evidence of a disease, eliminate the stigma, and remove migraine from its place of silence. Many neurologic diseases are very difficult to treat. Migraine may be an outlier, with huge benefits from appropriate treatments and more to come. The burden faced by individuals and society will be greatly diminished in a tangible manner by taking this condition seriously. In some ways it is akin to the benefits from smoking cessation, in that society will benefit on the order of hundreds of millions of person-days per year if migraine is "conquered" in the short term by appropriate funding for research, target validation, and drug development.

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