Cosensitization of Pain and Psychiatric Comorbidity in Chronic Daily Headache

Roger Cady, MD, Kathleen Farmer, PsyD, J. Kent Dexter, MD, and Curtis Schreiber, MD*

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Chronic migraine occurs in approximately 20% of migraineurs, typically developing over a period of many years. The pathophysiology of this transformation is unknown. However, experts have associated chronic headache with analgesic overuse, physical injury, and psychologic trauma. Research in post-traumatic stress disorder has found that hippocampal sensitivity to stress alters and often amplifies future pain behaviors. Although the most obvious difference between migraine and chronic migraine is the frequency of headaches, this article discusses chronic migraine as a more pervasive neurologic disease in which the patient's neurologic and psychologic function fails to return to a normal baseline. The sensory and affective components of pain are cosensitized, producing other neurologic and psychologic symptoms during and between episodes of headache. A staging paradigm is suggested that defines patients and assesses their overall neurologic function. The goal of this classification is to identify cosensitization early and pinpoint migraine patients who are at risk of developing chronic migraine.

Introduction

An estimated 28 million people in the United States suffer from migraine as defined by the International Headache Society (IHS) [1], while an estimated 4% to 6% (5.6 million) of the population has headache on a daily or near daily basis [2]. Most of the chronic headache population report clinical histories of migraine preceding the development of their daily headache patterns (1.5.1). According to the latest revision of the IHS criteria, "Most cases of chronic migraine start as 1.1, migraine without aura. Therefore, chronicity may be regarded as a complication of episodic migraine." IHS defines chronic migraine as "attacks of headache occurring on more days than not over a period longer than 3 months."

The impact of severe migraine on the world population as reflected in the Global Burden of Disease Study [3] is equivalent to the disability suffered by those with active psychosis, dementia, and quadriplegia (Disability Class 7). As suggested by the results of the study, although certain brain disorders may be labeled as psychiatric problems, in reality, they are diseases of the nervous system. By considering migraine as a neurologic disorder, the "chronicity" of chronic migraine has more neurologic implications than just the frequency of headaches.

Numerous psychologic and affective disorders are known to be comorbid with migraine such as depression, generalized anxiety disorder, and panic disorder [4,5]. The concept of comorbidity is based on epidemiologic studies that demonstrated a higher than chance association of the two disorders compared with their prevalence in the general population. It does not imply causality to the relationship, although several studies have raised the possibility of a causal relationship between migraine and psychologic comorbidities [4,5]. This is based partly on certain neurochemical mediators being shared in this spectrum of disorders.

This article explores the relationship of chronic migraine and psychologic comorbidities as being physiologically linked through a cosensitization of these disease states as a consequence of repeated pain experiences over time. In this sense, chronic migraine may be considered a pervasive rather than progressive neurologic disorder.

The Spectrum of Migraine

Episodic migraine is a self-limited paroxysmal attack that typically disrupts neurologic functioning for 4 to 72 hours. Between attacks of migraine, the nervous system presumably returns to normal baseline function. Clinical symptoms observed during acute migraine are characterized by moderate to severe localized pain that is aggravated by activity and throbbing in nature. This headache is associated with sensory hypersensitivity (photophobia, phonophobia, osmophobia, and cutaneous allodynia) and gastrointestinal disruption (anorexia, nausea, vomiting, and diarrhea). Many of these specific symptoms form the basis of the IHS diagnostic criteria for migraine without aura. In addition, episodes are associated with moderate to severe disability and often bed rest.

Although disability during an acute episode of migraine often is substantial, recovery generally is rapid and complete. If attacks are infrequent, lost productivity can be recovered easily in subsequent days. Thus, from this perspective, infrequent migraine is similar to a severe 24-hour flu syndrome and does not necessarily lead to medical evaluation and treatment.

The clinical description of the headache pain associated with episodic migraine is explained by patients in specific terms, which are anatomically localized [6]. The quality of pain likewise is described in precise terms such as throbbing, pounding, or extreme pressure. Repeated attacks often are symptomatically stereotypic. Thus, there should be little diagnostic confusion about a well-established pattern of infrequent episodic migraine. Unfortunately, these patients are not commonly evaluated medically for migraine because they often choose to self-manage attacks throughout their lifetime.

The Evolution of Chronic Migraine

If the episodic pattern of attacks becomes more frequent and chronic, the nervous system often fails to recover to a state of normal neurologic function between headache attacks. Patients often describe the emergence of a low-grade headache that can occur on a daily or near daily basis, over which is superimposed episodes of headache that are more migraine-like. Over time, the patient becomes increasingly headache prone to the point that attacks can be precipitated by even minor perturbations. The stereotypic nature of these headaches becomes less apparent. Retrospective studies suggest that it takes an average of 10.8 years to evolve from episodic to chronic migraine [7].

Beyond headache, other neurologic disruptions frequently punctuate the interval between episodes of headache such as anxiety, depression, sleep impairment, and other pain conditions particularly in the head, neck, and back [8]. This transition eventually identifies the disease state of chronic migraine. Analysis of epidemiologic studies would suggest that for one fifth of migraineurs, episodic primary headache may transition into a chronic headache disease at least at some point in their lives [9••].

Clinical Features of Chronic Migraine

Those with chronic migraine describe their headaches much differently than those with infrequent episodic migraine. In general, by the time headache sufferers have reached the point of seeking medical evaluation of their headaches, they believe they have several completely unique headache presentations. For example, in the American Migraine Study II [8], a group of 1604 respondents with a medical diagnosis of primary headache and IHS migraine by telephone interview reported on a mailed questionnaire that they considered themselves to have at least three unique headache diagnoses: migraine, sinus headache, and tension headache. This belief was independent of the medical diagnosis they had received. Furthermore, the more frequent the headaches, the more likely respondents were to have a primary headache diagnosis of tension headache, despite the fact that some of their headaches achieved migraine status by structured telephone interview. This underscores the varied nature of migraine symptoms and presentations in a population with frequent migraine who seek medical evaluation.

Chronic primary headache patients typically describe their headaches in less precise language than those with infrequent episodic migraine. The location of the pain is described as more diffuse, vague, or migratory and the quality and severity of the pain changes from day to day. Mathew [10] has noted that the associated symptoms also shift from autonomic and gastrointestinal in episodic migraine to musculoskeletal and psychologic in chronic "transformed migraine." Concomitantly, the emphasis of the patient shifts from recognizing migraine as an occasional disruption of daily life to the center piece of daily function. As patients remark, "My life revolves around headaches."

Medication also becomes a focus of attention and medical concern in the chronic primary headache population. Despite the significant impairment associated with an acute episode of migraine, episodic migraine often is self-managed with the use of over-the-counter or symptomatic products. Together with the knowledge that time and perhaps sleep will restore function, these individuals are satisfied if their medications simply allow them to get through an attack of migraine. Conversely, chronic migraine patients frequently make medication a centerpiece of daily life. They frequently use complex cocktails of a variety of analgesics, muscle relaxants, anxiolytics, antidepressants, and migraine preventive medications, all in the face of a continuing daily headache pattern. This has given rise to the concept of medication-overuse headache, implying that medication overuse can pharmacologically maintain a chronic headache pattern. Although most clinicians accept the premise of medication-overuse headache, this concept remains somewhat controversial because some studies suggest that discontinuation of offending medications does not necessarily improve headache patterns or quality of life [11•].

An estimated 20% of chronic primary headache disorders develop suddenly and are classified as new daily persistent headache [1]. However, at times, episodic migraine patterns transform into chronic migraine quite rapidly during a period of intense stress, psychologic trauma, or physical injury. Once established and persistent, daily headache syndromes are associated with significant changes in psychologic profiles. Mathew [10] found that 61% of daily headache patients had abnormal Minnesota Multiphasic Personality Inventory results compared with 12.2% of episodic headache sufferers. Whether this is a primary predisposing factor or an adaptive response to chronic headache is unknown.

In many ways, chronic primary headache is not simply an extension of episodic migraine. Beyond the obvious distinction of headache frequency, these syndromes differ clin-

ically in terms of the description of headache, the number and type of associated symptoms, response and dependence on pharmacology, and psychologic and behavior responses to pain. Further treatment approaches are quite distinct in that chronic primary headache patients often require interdisciplinary care when episodic headache patients typically respond well to straightforward, specific, pharmacologic intervention.

Chronic Migraine as a Pain Syndrome

Pain has been defined as an "unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in such terms" [12]. As such, pain is subjective with emotional and physical components. Acute pain is protective and provides warning of injury or the threat of injury that dictates corrective action. The duration of acute pain reflects the restoration of physiologic function and normal healing. For example, an acute attack of migraine is explained by its underlying pathophysiology, which is responsive to abortive pharmacologic intervention. As a result, the pain and associated symptoms resolve in a linear, scientific, logical process.

However, in chronic persistent pain, the relationship to injury or aberrant physiologic function is less clear. Chronic migraine lacks a clear adaptive benefit. Its relationship to the pathophysiologic process associated with acute episodes of migraine is unknown and treatment of chronic migraine with acute pharmacologic interventions is temporary at best. In fact, most centers in the Unites States that manage chronic primary headache patients support the use of interdisciplinary care models that go beyond simple pharmacologic intervention. Thus, in many ways, chronic primary headache disorders are more akin to a chronic pain syndrome than to unremitting acute migraine.

Anatomy of Pain Transmission

Migraine occurs episodically. It is presumed that the nervous system of the migraine patient is unique and physiologically more sensitive. For most, this sensitivity likely is determined by genetic factors, although behaviors and trauma (physical and psychologic) also may play a role. Migraine is manifested when this vulnerable nervous system encounters change in its environment (internal or external) that exceeds its homeostatic and adaptive capabilities. Theoretically, these triggering factors disrupt the neurochemical balance of the brain and lower the threshold of the nervous system to migraine. Electrical and neurochemical disruptions result in disinhibition of sensory processing mechanisms in the trigeminal nerve and brain stem. As the migraine process progresses, second- and third-order neurons in the central nervous system are disinhibited and sensory symptoms essentially are amplified by the disinhibited central mechanisms. Eventually, migraine has the potential to become an allodynic pain state. How the nervous system corrects the process of an acute migraine and re-establishes control is unknown. However, instrumental in driving and aborting the physiologic process of migraine are inputs from the trigeminal vascular system, brain stem, cortex, thalamus, hypothalamus, and limbic areas.

Episodic migraine follows a predictable progression as described by Blau [13] who differentiated the migraine attack into five clinical phases: prodrome, aura, headache, resolution, and postdrome. This expanded on earlier observations by Wolff [14] who delineated migraine into three phases: preheadache, headache, and postheadache. To further the value of identifying the phases of the attack of migraine, the Convergence Hypothesis redefined the range of clinically observed primary headaches as expressions of the central nervous system's evolution through the migraine process [15•]. The migraine process can resolve and be terminated at any point during its evolution, either naturally or through intervention with medication, exercise, biofeedback, simply removing oneself from the stressor, or by any method that has proven effective.

Pain Pathways

The transmission of pain occurs primarily in two distinct peripheral pathways through A-δ fibers and C-fibers [16•]. Small myelinated A-δ fibers transmit pain impulses to the trigeminal ganglia, thalamus, and eventually the primary somatosensory and cingulated cortices. Location of this type of sensory input is anatomically precise and discriminative.

However, the affective aspect of pain traverses the unmyelinated C-fibers and, through the thalamus, connects with the limbic cortex. In this case, the pain experience is integrated with a wide variety of central influences that impact the affective component of the pain response. In contrast to the precise discriminative pain interpretation observed from the somatosensory cortex, pain perception from the limbic cortex is affective, diffuse, and nondiscriminatory. Facilitatory and inhibitory influences descend from the limbic systems, which can markedly influence pain perception.

Each of these components of pain perception appears to have physiologic purpose. The somatosensory localization of pain ensures a precise and appropriate immediate response to threat, while the affective limbic response determines a more global response that puts the organism into a highly vigilant physiologic state, until the environment itself is assessed to be safe from further injury. In this way, there are dual responses to pain: sensory realization that the body needs to react quickly for its own well-being and affective reaction to an assault on the body designed to assess the environment for safety and create behavioral responses that help avoid the circumstances that were associated with the painful experience ("fight or flight" response).

After repeated stimulation of pain pathways, sensitization occurs, which decreases the threshold for depolarization. Sensitization happens on different levels, peripherally and centrally. The wind-up of central sensitization develops

when C-fibers, which communicate with the limbic system, are discharged by a sustained stimulus at a high frequency, producing a response rate of wide dynamic-range neurons that increases progressively after each stimulus [17].

As sensitization occurs through chronic pain, the plasticity of the nervous system produces changes (*eg*, A-fiber sprouting in the spinal cord) at multiple levels that alter pain modulation in favor of hyperalgesia and a perpetual state of vigilance. Allodynia or the response of neurons to subthreshold stimulation may result from hyperalgesia [17].

Cosensitization of Sensory and Affective Components of Pain

Nociceptive (pain) stimuli alert sensory and affective components of the nervous system. In migraine, the pain process is repeated many times over a period of many years. The migraineur often does not understand the cause of the attack or feels powerless to alter its impact. In this sense, migraine may be viewed as an uncontrolled traumatic event. This is made even more likely when one considers the psychosocial disruption migraine causes or that migraine often occurs during events with emotional charge. Migraineurs begin to fear when the next attack will occur and may take medicine "just in case" an attack strikes during an important activity.

The concept that powerful emotional events can alter future pain behavior has been studied best in the field of post-traumatic stress disorder (PTSD). Seminal research has attempted to explain why when exposed to the same trauma, certain individuals go on to develop PTSD while others do not. Since 1968 and the discovery of receptors for stress hormones (corticosteroids) in the rodent hippocampus [18], considerable data on the role of the hippocampus in stress reactivity have been gathered. Hippocampal sensitivity to stress has been extrapolated to explain the negative impact of stress and related stress hormones on animal and human cognitive function. Chronic states of stress essentially lead to heightened levels of glucocorticoids, which cause the death of cells associated with new memory and learning in the hippocampus [19]. Trauma and psychosocial stress can lead to a suppression of neurogenesis and growth processes in primate brains [20] that may be manifested as the psychologic experience of depression in humans [21].

Other studies of those with PTSD found that these individuals had less brain volume than control subjects. Considering that bone development stops after adolescence, the smaller size of the cranium of those with PTSD would indicate that trauma previous to the episode associated with PTSD must have occurred before adulthood. Corticosteroids have been associated with a reduction in birth weight and head circumference among newborns [22] and with persistent deficit in bone mass among adolescents [23]. Children's salivary cortisol levels are significantly correlated with the mother's extent of depressive symptomatology [24]. Stressful events produce biologic-hormonal changes that may result in physical alterations in the brain. This process potentially sets the person up to misinterpret impulses coming into the limbic lobe as pain. The response becomes stereotypic, the world shrinks, and the person feels trapped, frantic, and afraid.

In the extreme cases, pain becomes internalized. A sense of helplessness takes over. A wrestling match embattles person against pain, made more desperate by terror that pain will win. Eventually, fear dominates and the chronic headache sufferer feels surrounded by a sense of hopelessness. Can these symptoms be diagnosed as depression, anxiety, or panic disorder or are they manifestations of a chronic neurologic dysfunction [25,26]?

Association of Traumatic Events and Chronic Primary Headache Disorders

Those with chronic daily headache often state that any change in the environment, external or internal, produces a headache. Their lives revolve around headaches. Headache becomes the stereotypic response to change. In this way, the normal psychobiologic arousal that acute pain produces in the limbic lobe becomes pathogenic stress when it persists over time because of an apparent loss in the ability to turn off the mind-body's arousal hormones and maintain optimal homeostasis and adaptation.

In this way, sensory and affective pain pathways become sensitized. Because of previous experiences or memory of a painful stimulus within an environmental context, there is an augmented response. Neuroplastic changes develop in the corticolimbic system yielding the clinical presentation of persistent pain, affective dysregulation, and behavioral disturbance. This has been labeled limbically augmented pain syndrome [27]. Individuals experiencing limbically augmented pain are characterized by atypical and treatment-refractory pain complaints, in association with disturbances of mood, sleep, energy, libido, memory/concentration, behavior, and stress intolerance. This likely describes many patients with chronic migraine seen at headache specialty clinics.

Migraine as a Pervasive Neurologic Disease

Migraine as a progressive neurologic disease has been the subject of significant debate. As the attack of migraine advances, there clearly is progressive sensitization of the nervous system as the process evolves from peripheral to central sensitization. However, with resolution of the (infrequent) acute episode, the nervous system appears to return to normal and, although migraine can become more chronic for decades of time, it generally improves later in life. However, in a significant subset of clinically defined migraine patients, there also appears to be a progression of other neurologic conditions that accompany migraine as it evolves from an episodic to a chronic condition.

This transformation is amplified by the occurrence of many comorbid conditions that are particularly apparent

Table 1. Stage patient examples that are in medical offices

How many days per month do you have headaches?
Stage 4: Fewer than 10
Stage 6: 10 to 20
Stage 7: Daily headaches; constantly
Does your prescribed medication stop them?
Stage 4: Yes, most of the time
Stage 6: It takes the edge off, but the headache is still there
Stage 7: Nothing works
Do you have physical problems other than headaches?
Stage 4: No, I am healthy
Stage 6: I have some aches and pains, but my biggest concern is my headaches
Stage 7: Yes, depression, fibromyalgia, insomnia, irritable bowel syndrome, obesity; I am falling apart
How do your headaches interfere with your life?
Stage 4: They are a nuisance, but I force myself to go on
Stage 6: I am missing work or my child's activities once in a while
Stage 7: My life resolves around headaches

as episodic migraine becomes more frequent and chronic. However, it also is true that chronic migraine can revert to its episodic form spontaneously and that, over time, it appears to improve or actually resolve. This is supported by epidemiologic evidence that the prevalence and incidence of migraine diminishes with age. Thus, one could assume that there are no or few long-term sequelae to migraine.

However, as a pervasive disorder, the focus is shifted from a linear time model to temporal severity model. This implies that the burden of disease at any point in time is based on a global evaluation of nervous system function. From this vantage point, migraine robs decades of quality from people's lives because of headaches and other associated diseases and the depth to which it disrupts overall neurologic function.

Conclusions

The sensory and affective components of nociceptive input generated during acute migraine are interpreted by an individual as pain. However, current diagnostic and therapeutic criteria are focused almost exclusively on the sensory component alone. Thus, clinicians diagnose migraine by eliciting from the patient's history unilateral, throbbing headache that is moderate to severe in intensity and aggravated by activity and gauge therapeutic success by resolution of the same symptoms.

The affective (limbic) component of migraine pain essentially is ignored in terms of formal diagnosis and clinical study. Many clinicians assume that the affective aspect resolves when the sensory component of migraine pain is alleviated. For centuries, astute clinicians have understood and described the affective symptoms accompanying migraine, but have failed to introduce these factors into academic study of migraine. However, clinical analysis of the migraine patient suggests that these affective symptoms may not resolve with treatment of the acute attack and actually may persist in disrupting neurologic function between attacks of IHS migraine. If these symptoms are not addressed, they can coalesce over time into discrete psychologic diagnoses that frequently are considered comorbid with migraine.

This cosensitization model suggests that migraine is a pervasive neurologic disease. Although early episodes of migraine resolve to normal neurologic function, repeated episodes may sensitize the nervous system over time in a manner that reflects ongoing neurologic disruption. Affective components of migraine, such as a heightened sense of vigilance, fear of next attack, worry over inability to function, feelings of isolation, and letting others down, undermine the homeostasis of the nervous system, increasing headache frequency, emotional sequelae, and powerlessness to function. This observation underscores the need to expand diagnostic evaluation to the patient with migraine, not simply the headache. Clinical experience dictates that it often is the nonheadache factors that complicate migraine management. This implies the need for a classification or staging paradigm that defines patients and assesses neurologic function between headaches. This process will identify cosensitization early, pinpointing migraine patients at risk of transforming into chronic migraine [9••]. This allows for more comprehensive and holistic approaches to care for the migraine patient.

Based on clinical interviews of patients with headaches and a wide range of Headache Impact Test and Migraine Disability Assessment scores, descriptions of the impact of headaches on their lives ranged from stage 1, no impact, through stage 7, chronic migraine with polypharmacy and complaint, "There is no life beyond my headaches." These seven stages trace the escalating cosensitization of the nervous system and psychologic reactions to constant head pain. Patients in stages 1 through 3 usually do not seek medical consultation for headaches. Table 1 provides several staged patient examples that are seen in medical offices.

Cosensitization classifies psychiatric comorbidities as part of the pervasive neurologic entity defined as chronic migraine. These affective responses to nociceptive input

(pain) are indications that the process of migraine transformation is occurring and that migraineurs feel helpless to reverse chronic headaches. Even when the headache subsides, the person is living in a constant prodrome of fatigue, irritability, lethargy, discouragement, and feeling victimized. Rather than a crystallized psychiatric disorder, this psychologic cosensitivity is a reaction to an unsuccessful pursuit for help for relentless headaches.

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