The under-recognized but essential role of the limbic system in the migraine brain: a narrative review

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ABSTRACT

Migraine is a very common brain disorder that causes throbbing headaches of moderate-to-severe intensity that are associated with a variety of symptoms like nausea, vomiting, multisensory hypersensitivity, dizziness, fatigue, cognitive dysfunction, and sleep problems, among others. The diverse symptomatology of migraine hints at the complexity of the disease and implies the involvement of multiple nervous system components, including the somatosensory, executive, autonomic, endocrine, and arousal networks. The major pathophysiologic mechanisms responsible for migraine attacks have been identified over the past several decades, and the elucidation of these mechanisms has brought about remarkable advances in therapeutic strategies, including the creation of anti-calcitonin gene-related peptide therapeutics—the newest addition to the list of anti-migraine therapies. However, current knowledge on the pathophysiologic mechanisms of migraine remains incomplete and treatments are only partially effective, with the involvement of the limbic system being less often recognized and symptoms related to the limbic system being undertreated. This article reviews recent advances in understanding the pathophysiologic roles of the limbic system in migraine and how the limbic system contributes to clinical features observed in migraine.

Keywords: Cognitive dysfunction; Comorbidity; Headache; Limbic system; Migraine disorders

INTRODUCTION

Data from the 2016 Global Burden of Disease study show that migraine affects approximately 1.04 billion people worldwide, causes greater disability than any other headache disorder, and ranks second among the most disabling neurologic disorders after stroke [1]. Recurrent, painful headaches are the most agonizing and burdensome problem in individuals suffering from migraine. However, migraine is also associated with a variety of non-headache symptoms such as dyspepsia, photophobia, phonophobia, cognitive complaints, and increased pain perception during and between migraine attacks [2]. The constellation of symptoms associated with

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migraine suggests that it is mediated not only by neural networks responsible for pain, but also by pathways involved in visual, auditory, autonomic, endocrine, psychological, behavioral, cognitive, and arousal functions [3]. From this perspective, migraine can be regarded as a multifaceted disorder involving numerous brain networks [4]. Furthermore, it is essential to recognize, understand and manage these non-headache symptoms that might modify the long-term clinical course of migraine and further reduce the quality of life (QoL) for patients with migraine. In this review article, the authors aimed to provide update on recent advances regarding the pathophysiologic roles of the limbic system in migraine and the contribution of the limbic system with regards to clinical features observed in migraine.

THE PATHOPHYSIOLOGY OF MIGRAINE HEADACHE

The complex neurobiological mechanisms that underlie the development of headaches in the migraineur's brain and the responsible neural pathways are relatively well defined [5]. The trigeminal neurovascular system is a key component of the migraine headache, consisting of sensory afferents that innervate the meninges and intracranial vasculature, the three branches of the trigeminal nerve that innervate the face and anterior head, the trigeminal ganglion, and the trigeminal nucleus caudalis of the brainstem. Ascending projections from the trigeminal nucleus caudalis project to the thalamus and then to multiple regions of the cerebral cortex and cerebellum that participate in sensory discriminative, affective, cognitive, and integrative aspects of the pain experience. The peripheral and central components of this system can become sensitized during and perhaps even between migraine attacks, lowering the threshold for activation and resulting in cranial and extracranial allodynia [3,5].

Activation of the trigeminovascular system is associated with the release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), a potent vasodilator that plays a major role in the generation and facilitation of pain and pain-related symptoms in migraine. Along with release of CGRP there is release of other vasoactive neuropeptides, dilation of the meningeal vessels, extravasation of plasma proteins, and degranulation of mast cells. Numerous proinflammatory mediators are then released, promoting neurogenic inflammation and stimulation of meningeal nociceptors. Eventually, the pain circuits of migraine are perpetuated [6,7].

Anti-CGRP monoclonal antibodies that block either the

CGRP receptor or ligand were approved by regulatory agencies and were launched in the USA and Europe in 2018 and in Korea in late 2019 for migraine prevention. Small molecule CGRP antagonists were approved for the symptomatic therapy of migraine attacks in the USA in late 2019 and early 2020. A large body of pre-clinical and translational research and the efficacy of these CGRP-blocking therapies in clinical trials confirm the role of CGRP in migraine [3,8-12].

Despite successes in the development of novel migraine-specific agents, there is still need for even more effective migraine therapies [13]. In general, about 50% of patients will respond to any one migraine preventive medication, and the response is almost always less than complete, meaning that there continue to be recurrent migraine attacks albeit with a lower frequency. This suggests that the mechanisms underlying migraine are multifactorial within and between patients. Inadequate preventive and symptomatic therapy results in greater migraine-related burden and a higher risk for developing chronic migraine and an associated condition called "medication overuse headache (MOH)." Given the current state of migraine therapeutics, a more holistic approach to treatment is required, with therapies that target the pain pathways and other mechanisms that lead to the non-pain symptoms and comorbidities of migraine.

THE NON-PAIN FEATURES OF MIGRAINE

Migraine headaches are often accompanied by a variety of non-pain symptoms such as photophobia, phonophobia, gastrointestinal dysfunction, cognitive complaints, and increased pain perception that increase the burden of the disease, decrease the QoL, and worsen the long-term clinical course for many people with migraine. Many of these non-pain symptoms seem to originate from dysfunction of the limbic system and its associated neurolimbic networks [14].

A dysfunctional limbic system presents with aforementioned non-pain symptoms at every phase of a migraine attack, including the prodromal, ictal, and postdromal (or hangover) phases, as well as during the interictal period [2]. The limbic system is strongly associated with the catastrophizing and migraine chronification that often leads to MOH [15].

Two recent studies (migraine in America symptoms and treatment [MAST] [16] and Chronic Migraine Epidemiology and Outcomes [CaMEO] [17]) have shown that patients with migraine reported a significantly higher prevalence of comorbid conditions such as insomnia, depression, anxiety,

Table 1. The neurolimbic comorbidities of migraine

System	Specific conditions	References
Psychiatric disorders	Depression, anxiety, panic disorder, bipolar disorder, personality disorders, stress, suicide attempts	[16-29]
Sleep disorders	Insomnia, parasomnias, restless leg syndrome, sleep apnea, poor sleep quality and duration	[30-35]
Chronic pain	Fibromyalgia	[36-40]
Epilepsy	Seizures, independent of type	[41-44]
Cognitive dysfunction	Memory changes	[45-47]

gastric ulcers/gastrointestinal bleeding, angina, and epilepsy. The presence of more comorbidities was associated with increasing headache intensity and frequency. In clinical practice, it is often observed that certain prophylactic agents that act on the limbic system are quite effective in patients who present with neurolimbic comorbid symptoms (authors' experience). Table 1 lists the major neurolimbic comorbidities of migraine [16-47].

ANATOMIC BASIS OF NEUROLIMBIC COMORBIDITIES

The limbic system consists of several regions including cingulate cortex, parahippocampal gyrus, hippocampal formation, amygdala, septal area, and hypothalamus. This system relays and integrates multiple inputs from both the body and the environment and filters or modulates the generation of emotional, homeostatic, and cognitive responses. The limbic system is composed of structures that are involved in specific functions such as the regulation of hunger and thirst; sexual satisfaction; and responses to pain, pleasure, and sensory information, particularly from the olfactory system. This system is also responsible for controlling aggressive or violent behavior, emotions such as anger and fear, and the functions of the autonomic nervous system, which include the regulation of pulse rate, blood pressure, breathing, and arousal. Because the limbic system functions as an “alarm system” of the brain, it may also be the first group of neural networks that recognize the start of migraine-related brain activities [14,48].

The somatosensory neural networks responsible for generating pain during migraine attacks pass mainly through the posterior part of the brain, including the trigeminocervical complex in the brainstem, thalamus, somatosensory cortex, and other cortical and cerebellar regions [5]. On the other hand, the networks responsible for neurolimbic features, particularly those that are emotional or psychiatric in nature, are located in the middle (hypothalamus and anterior cingulate cortex), medial temporal (amygdala and hippocampus),

and anterior (prefrontal cortex) parts of the brain [14]. In these regions, serotonin plays a key role in the neurobiological mechanisms behind the emotional or psychiatric comorbidities observed in patients with migraine; however, the exact role of serotonergic mechanisms in the brain in this context remains a matter of controversy [49].

It is possible that the limbic system might contribute to the development of higher frequency migraine (e.g., chronic migraine), medication overuse, and to MOH; however, despite its possible contributions to the clinical features of migraine, there have been few studies, both in scientific research and in clinical practice, on the limbic system in this context.

From a therapeutic viewpoint, it should be noted that bidirectional connections exist between the pain-modulating circuits of the brainstem and the limbic system, including the prefrontal cortex; these connections mutually influence the expression of migraine. Thus, any imbalance in this bidirectional neurolimbic system, as in a migraine brain, can modify the neurolimbic environment and affect the patient's mood, emotions, stress, personality, or coping styles, thus enhancing their vulnerability to migraine disease and migraine attacks [14]. The interplay between the neurolimbic system with the somatosensory system and the extent of dysfunction of these systems likely impact the presentation of migraine.

In this respect, the authors propose that neurolimbic symptoms should be assessed and considered when diagnosing and managing patients with migraine. Doing so allows for a more holistic approach to the patient with migraine and can lead to optimization of patient outcomes. Therapeutic strategies, either pharmacologic or non-pharmacologic, that target somatosensory and neurolimbic factors must be designed and tested through clinical trials to create more effective abortive and prophylactic treatments for migraine. Thus, it is strongly advised to screen for comorbid factors in all patients with migraine, particularly in refractory cases, and to consider these factors in the diagnostic and therapeutic planning [14,50]. Identifying the individual pathophysiologic mechanisms that underlie comorbid symptoms or conditions will

allow for the management of patients to be individualized and adjusted accordingly. Such approaches would be valuable in improving the treatment of migraine and its related problems.

FUNCTIONAL AND STRUCTURAL CHANGES IN THE LIMBIC SYSTEM IN CHRONIC MIGRAINE

Chronic migraine has a worldwide prevalence of 1% to 2% [51,52]. Several factors increase the risk of transforming from episodic migraine to chronic migraine, which is defined as 15 or more headache days per month including at least 8 days with migraine attacks per month; these include the overuse of acute pain/migraine medications, caffeine consumption, poor sleep hygiene as may be indicated by snoring, obesity, inadequate treatment of acute migraine attacks, lack of physical exercise, female sex, allodynia, head injuries, low socioeconomic status, depression, anxiety, stressful life events, post-traumatic stress, and comorbid pain disorders. Many of these factors have psychological components and might be associated with limbic system dysfunction [53,54].

Overuse of acute medications used to treat migraine attacks (triptans and ergots) or other pain conditions (opioids, non-steroidal anti-inflammatory agents, and combination analgesics) can increase the risk of someone with episodic migraine transforming to chronic migraine. Patients can find themselves in a vicious cycle that starts with headaches leading to increasing acute medication intake which then causes even more frequent headaches and greater medication use. Recent imaging studies have shown that overuse of acute migraine medications or psychotropic agents is associated with functional and anatomic changes in the limbic system [55].

In patients with MOH, resting state functional connectivity is decreased between the precuneus and the regions of the default mode network (DMN) (the frontal and parietal cortices) while it is increased between the precuneus and hippocampal/temporal areas. Functional connectivity between precuneus and frontal regions are negatively correlated with migraine duration and positively correlated with self-evaluation of medication dependence. Grey matter volumes (GMVs) of the precuneus, hippocampus, and frontal regions are also negatively correlated to migraine duration. Functional connectivity within the DMN is correlated with the anxiety scores of patients with MOH, while GMV in this network are associated with depression scores [55,56].

In another study on MOH patients, it was found that the volumes of the superior temporal, fusiform, and occipital middle gyrus of the left hemisphere were decreased while the volume of the left inferior temporal/lateral ventricle and middle frontal sulcus were increased. The left temporal superior gyrus volume was negatively correlated with depression scores, number of medications taken per month, and medication dependence scores [57].

Magnetic resonance imaging studies revealed that, in patients with MOH, the fiber tracts passing through the left hippocampus and the volume of anxiety-related hippocampal subfields were decreased. Changes in the grey matter of the brain were also observed in patients with MOH who also have psychiatric comorbidities like anxiety and depression. Furthermore, the volume of the periaqueductal grey matter of the midbrain was also significantly increased in these patients, which was positively correlated with more migraine-related disability and higher levels of anxiety. An increase in GMV was also found bilaterally in the thalamus and ventral striatum, while a significant decrease was detected in the frontal regions including the orbitofrontal cortex, anterior cingulate cortex, left and right insula, and precuneus [57-59]. The changes of structure and function in pain processing regions might be reversible and normalized following discontinuation of the overused medication and proper treatment of MOH [60].

CONCLUSION

The limbic system of patients with migraine appears to be perpetually involved during the course of the disease, even when the classical trigeminal neurovascular system is at rest [61]. The limbic system is responsible for non-headache symptoms and comorbidities of migraine that are commonly present and contribute to long-term patient outcomes. Neurolimbic symptoms and comorbidities remain poorly assessed and underemphasized in migraine, and therapeutic strategies for these symptoms also remain underdeveloped and underutilized.

Neurolimbic system-mediated symptoms and comorbidities contribute to the chronification of migraine and impact the patient's QoL and treatment satisfaction. Therefore, therapeutic strategies that stabilize or balance the neurolimbic system are required; these include psychological supportive care (mindfulness training), lifestyle modifications, and more aggressive pharmacologic and non-pharmacologic therapies such as cognitive behavioral therapy, acceptance-commit-

ment therapy, and narrative medicine. Finally, neurolimbic symptoms and comorbidities must be recognized when diagnosing migraine and the impact of migraine therapies on these symptoms and comorbidities must be closely monitored.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conception or design: CSC, TJS.

Acquisition, analysis, or interpretation of data: CSC, TJS.

Drafting the work or revising: CSC, TJS.

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