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Chronic migraine: A process of dysmodulation and sensitization

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Abstract

Chronic migraine is a common chronic daily headache featured by frequent headache attacks with at least 15 headache days per month, which brings great disease burden to both the sufferers and the society. Transformed from episodic migraine, the pathophysiology of chronic migraine is not fully understood, even though several risk factors have been associated with migraine progression. Recent studies have identified both structural and functional alterations in some brain regions of chronic migraine patients indicating that maladaptation of the top-down pain modulation and subsequent sensitization of trigeminal system may be important in the pathogenesis of chronic migraine. Moreover, biochemical analysis has confirmed several molecules related to chronic migraine, which may serve as biomarkers and potential therapeutic targets. Chronic migraine is undertreated because of its poor treatment response and limited therapy options. In this article, we reviewed the latest data to outline the clinical feature, pathophysiological mechanism, and management of chronic migraine, in the expectation to provide direction for future research and finally to take good care of chronic migraine patients.

Keywords

Chronic migraine, top-down modulation, central sensitization, biomarker

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Introduction

As one of the most common chronic daily headache (CDH) disorders, chronic migraine (CM) is featured by frequent headache attacks with at least 15 headache days per month.[1] Sufferers of CM usually have a history of episodic migraine (EM) and their headache frequencies increase with time. It is estimated that approximately 3% EM patients evolve to CM per year,[2] and similar result was obtained in a three-month follow-up.[3] Besides, this transformation is bidirectional with about 26% of CM patients remitting to EM in a two-year follow-up,[4] which makes it difficult to confirm the accurate prevalence of CM. With the increasing headache frequency, CM becomes less intense and more featureless, but is associated with worse treatment response. Both the undertreated headache and associated comorbidities cause greater disease burden for CM compared with EM.[5–7]

Although regarded as the same spectrum illness with EM,[8] the detailed pathophysiology of CM is not fully understood. The latest data have recognized several predisposing factors, such as medication overuse, insufficient migraine prophylactic treatment, low socioeconomic status, stressful events, and so on.[4,9] Moreover, recent neurophysiological and imaging studies have indicated that CM may be associated with both structural and functional alterations in some brain regions, especially the cortical hyperexcitability and brainstem dysfunction.[10–12] Sensitization of the trigeminal system also play a vital role, as allodynia is quite common in CM patients.[13] Besides, several molecular mechanisms have been indicated to be involved in the pathogenesis of CM, such as calcitonin gene-related peptide (CGRP), serotonin (5-HT) system, pituitary adenylate cyclase activating polypeptide (PACAP), and so on.[14–16]

With the high disability rates and confusing pathogenic process of CM, management of the disease is still

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a big challenge for clinicians up to now. The treatment choices are quite limited and only few is well evidence-based. The most accepted options include topiramate, onabotulinumtoxin A, and some neuromodulation therapy patterns.[17–20] In this article, we reviewed the latest data to outline the clinical feature, pathophysiological mechanism, and management of CM, in the expectation to provide direction for future research and finally to take good care of CM patients.

Clinical aspects of CM

The diagnostic criteria of CM have evolved during the last two decades. The concept of CM was first defined in the International Classification of Headache Disorders second edition as "patients suffering from at least 15 migraine days per month for at least 3 months without medication overuse."[21] Then, in 2006, the diagnosis of CM was broadened as "headache (tension-type and/or migraine) on $\geq$15 days per month for at least 3 months without medication overuse, of which at least 8 days are migraine."[22] It was further broadened in the International Classification of Headache Disorders third beta version, as medication overuse headache (MOH) is no longer exclusive to CM.[1] The diagnosis of CM mainly depends on history taking, but it is usually difficult for patients to recall of past headache attacks especially for those with headache for years. Therefore, the clinical diagnosis of CM is challenging, and objective auxiliary diagnosis measures are in need such as the biomarkers, imaging diagnosis model, and so on.[23]

The accurate prevalence of CM is unknown as different diagnostic criteria were used in previous studies, and the dynamic transformation between CM and EM also make it difficult. As estimated, the prevalence of CM is about 2% in general population, which is lower in Asia population.[24,25] CM is associated with greater disease burden compared with EM, as illustrated in its higher disability rates, more disease cost, and increased rates of psychiatric comorbidities.[26–29] In two large-scale longitudinal cohort studies about CM, the Chronic Migraine Epidemiology and Outcomes Study and American Migraine Prevalence and Prevention Study, CM patients got higher scores in both the Migraine Disability Assessment Scale and the Headache Impact Test-6, indicating that CM is more disable than EM.[6,30] CM is also more likely to be associated with both psychiatric and somatic comorbidities, which further enlarges its impact. According to the American Migraine Prevalence and Prevention study, more CM patients met the diagnostic criteria for depression or anxiety disorder than those of EM.[31] In addition, other chronic pain conditions, respiratory diseases, and cardiovascular events were more common among CM patients.[7]

Recent studies have reported some risk factors for migraineurs progressing to CM, such as female gender, low socioeconomic status, obesity, baseline headache frequency, medication overuse (MO), insufficient headache relief and prophylaxis, stressful events, comorbid pain, and so on.[3,9] More than half of CM were reported to overuse medication, and use of barbiturates and opiates has been especially associated with increased risk of CM.[25] However, the causal relationship between CM and MO is still in debate.[32] Meanwhile, inadequate acute headache treatment was also found to contribute to new onset CM.[2] Therefore, appropriate acute therapeutic choice and sufficient prophylaxis is very important for preventing migraine chronification. The comorbidity of depression/anxiety also promotes transformation of migraine, indicating the bidirectional relationship between depression/anxiety and migraine.[31]

Pathophysiology of CM

Up to now, the pathophysiological process of migraine is not fully understood, and the same to CM. However, all recent data indicate that migraine is a disorder of brain dysfunction with both the genetic background and environment triggering.[33] Transformed from EM, the pathogenesis of CM is also related to the brain. And recent evidence has proved both structural and functional alterations in brain, especially the cortical hyperexcitability and abnormities in brainstem.[12] Larger proportion of CM patients reported cutaneous allodynia than EM ones,[34] illustrating that sensitization of trigeminal system involves in the development of the disease. In addition, several molecules, such as CGRP and 5-HT,[14,15] have been reported to be correlated with migraine chronification. In this article, the latest data were reviewed and the pathophysiological model was outlined (Figure 1). In brief, both recurring headache attacks and the comorbid conditions (medication-overuse, anxiety, and depression) promote the derangement of top-down pain modulation and also atypical release of nociceptive molecules, which aggravates trigeminal sensitization induced by repeated nociceptive inputs. With this hypersensitive state, the EM finally progresses to a "never-ending" condition, namely, CM. To be noted, the neural plasticity induced by the risk factors of CM may influence themselves in turn.

Dysfunction in top-down pain modulation

Cortical hyperexcitability. With the development of electrophysiological and neuroimaging technique, lots of recent studies have focused on the responsivity in CM brain. Generally, studies of cortical responsivity tend to indicate an increase in excitability, in particular of somatosensory and visual cortices.[35]

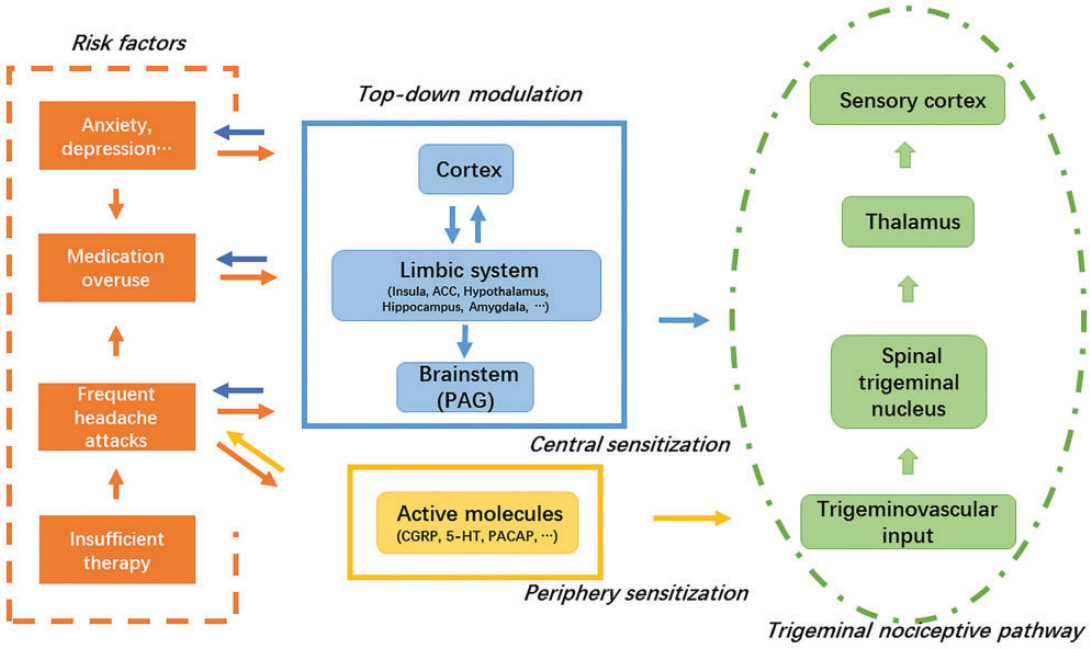

Figure 1. The proposed pathophysiological process of chronic migraine (CM). Both recurring headache attacks and other risk factors for migraine transformation (medication-overuse, anxiety, and depression) promote the derangement of top-down pain modulation and also atypical release of nociceptive molecules, which aggravates trigeminal sensitization induced by repeated nociceptive inputs. With this hypersensitive state, the episodic migraine finally progresses to a "never-ending" condition, namely, CM. To be noted, the neural plasticity induced by the risk factors of CM may influences themselves in turn. ACC: anterior cingulate cortex; PAG: periaqueductal gray; CGRP: calcitonin gene-related peptide; 5-HT: serotonin; PACAP: pituitary adenylate cyclase activating polypeptide.

In a transcranial magnetic stimulation study, excitability of the cortex of CM patients was assessed by magnetic suppression of perceptual accuracy profiles.[10] And CM sufferers exhibited reduced visual suppression than both EM patients and normal controls, indicating the existence of cortical hyperexcitability. Subsequent positron emission test scan of part of the same cohort found increased metabolism in brainstem and decreased metabolism in the medial frontal and parietal as well as the somatosensory cortex.[10] This brainstem activation and inhibition in certain cortical areas of the cortex maybe interpreted as a potential dysfunction in the inhibitory pathways, which induces increase in cortical excitability and finally the migraine transformation.

CM patients also demonstrated a persistent ictal-like excitability pattern of the visual cortex between migraine attacks according to visual evoked potential assessment,[36] suggesting that evolution of CM is consistent with alteration of central excitability and that CM is a status of "never-ending" migraine. In a positron emission test analysis of CM combined MO patients, altered metabolism were also found in similar pain-related cortical regions, and these changes remitted to normal after successful analgesic withdraw therapy.[37] To be noted, functional and metabolic changes in the prefrontal cortex are especially correlated with MOH, which may be a newfound brain region in pain-modulation in MOH.[38] All these data support the claim that these pain-related changes are related with both frequent headache attacks and medication overuse and may contribute to migraine chronification.

Also, the structural change of cortex has been studied among CM patients, including the gray matter volume and cortical thickness.[11,39–42] However, relatively small sample sizes were included in these researches and no consistent results were obtained. The mechanisms underlying the structural alterations remain to be elucidated. In addition, further longitudinal data are needed to determine the causal-consequence relationship between these functional/structural alterations and migraine chronification.

Brainstem alterations, especially the periaqueductal gray. As an important part of the top-down regulation of pain, the brainstem exerts descending modulation of the trigeminal nuclei and associated sensory and motor response in migraine, and also interacts with other cortical and subcortical areas. To date, migraine has been associated with this altered endogenous descending pain-modulation in brainstem by a number of studies, of which the periaqueductal gray (PAG) attracted the most attention.[8,10,12] Receiving inputs from frontal cortex, hypothalamus, and other supraspinal structures, PAG is the center of the descending pain-modulation

network via projections to the rostral ventromedial medulla, which can either inhibit or facilitate pain transmission through direct projections to the spinal and medullary dorsal horn.[43]

Several clinical observations have indicated the possible role of PAG in migraine generation, and the dysfunction of this brain region may also be associated with migraine transformation.[44,45] A resting-state fMRI has confirmed that migraineurs showed stronger connectivity between PAG and several brain areas within nociceptive and somatosensory processing pathways with the increasing headache frequency. In contrast, the strength of the connectivity between PAG and pain modulation regions (prefrontal cortex, anterior cingulate, and amygdala) was weaker.[46] These data reveal an impairment of the descending pain modulatory circuits in the process of migraine transformation, leading to loss of pain inhibition and hyperexcitability in nociceptive areas. Similar atypical functional connectivity of the PAG with brain regions involved in nociception, somatosensory processing, emotional processing, and pain modulation has been revealed in rats induced by repeated meningeal inflammation,[47] indicating that this brainstem dysfunction may be the consequence of recurring headache attacks. Meanwhile, medication-overuse also aggravates the maladaptation of descending pain-modulation.[48] Chronic morphine exposure has been proved to induce both loss of diffuse noxious inhibitory controls[49] and increase in descending pain-facilitation.[50]

Aside these functional alterations, involvement of PAG in migraine chronification has also been demonstrated through iron homeostasis impairment[44] and gray matter density alteration.[51] Increased tissue iron represents a disturbed functional state of neuron. And by high-solution MRI, significant increase in tissue iron levels has been found among both EM and CDH patients compared with control subjects.[44] The iron homeostasis in the PAG was persistently and progressively in EM and CDH, manifesting that iron accumulation in PAG may have resulted from repeated attacks, possibly caused by free radicals generated during repeated migraine attacks.[52] It is also worth noting that tissue iron levels tend to be higher than normal at the outset of migraine-susceptible,[44] indicating the causal role of iron homeostasis impairment in migraine and its transformation. Furthermore, in a recent volume analysis of PAG in migraine, EM patients showed a larger PAG volume than healthy controls, with that of CM in between, which may be considered as a diagnostic and evaluated imaging biomarker for migraine.[53]

Other brain regions. Besides the somatosensory processing, migraine also includes emotional, autonomic, and cognitive aspects. From this perspective, some studies have focused on anterior cingulate cortex (ACC), hypothalamus, insula, hippocampus, amygdala, and other brain regions related to the limbic system.[54–56]

By resting-state functional connectivity analysis, CM was associated with interictal atypical functional connectivity with affective pain regions which included regions in anterior insula, amygdala, pulvinar, mediodorsal thalamus, middle temporal cortex, and PAG, which significantly correlated with disease duration.[57] This atypical functional connectivity may relate to aberrant affective pain processing and atypical affective responses to painful stimuli in CM. Structurally, CM (including MOH) patients showed a focal gray matter decrease in the bilateral ACC, left amygdala, and bilateral insula than these of EM.[23] In particular, there was a significant correlation between headache frequency and ACC alteration. ACC has always been acknowledged to involve in the affective dimension of pain, while recent evidences also support its role in the descending modulation of spinal nociception.[58,59] Recently, an abnormal pattern of hypothalamic hormonal secretion has been discovered in CM patients as shown by a chronobiological dysregulation and a possible hyperdopaminergic state,[60] supporting the involvement of the hypothalamus in the pathophysiology of CM.

Although no significant difference in the volumetric analysis of hippocampus and amygdala were found between migraineurs and healthy controls, a bidirectional correlation between headache frequency and volume of these two regions was confirmed among patients with migraine, with a peak at moderate-frequency (about 5–7 days/month).[55] This structural plasticity linked to headache frequency may represent the process from adaption to maladaptation, with respect to both the painful and emotional aspects of migraine. Abnormal functional connectivity of bilateral amygdala has also been observed in CM patients compared to that of EM, which is correlated with the score of sleep quality,[61] indicating the possible role of neurolimbic pain-modulating in the migraine chronicization.

The above-mentioned brain regions are related to pain-modulation, but are more important in the regulation of mood, sleep, visceral activities, learning, and so on. Meanwhile, CM is a complex syndrome with many associated conditions including acute medication overuse, anxiety disorder, depression, insomnia, and so on.[7] Furthermore, significant change of regional cerebral blood flow in the dorsal rostral pons, ACC, cuneus, and left pulvinar has been found among CM, which can be modified by suboccipital stimulation, an effective therapeutic choice for CM patients,[54] suggesting a role for these structures in the pathophysiology of CM and also possible targets for CM therapy. Thus, based on above evidence, we can speculate that frequent headache attacks cause maladaptation of these regions of the limbic system, which in turn exacerbates headache and

headache-related comorbidities, such as anxiety, depression, sleep disorder, and so on.

Sensitization of trigeminal system

A series of clinical observations have indicated that CM patients are hypersensitive. On one hand, cutaneous allodynia is more common and more severe in CM compared to EM and other primary headaches, which is a risk factor for migraine progression.[34] One the other hand, CM patients have lower pain thresholds than EM patients, as measured by quantitative sensory testing.[62] Cutaneous allodynia, a condition featured by feeling of pain elicited by ordinary nonpainful stimulation to skin, is regarded as the result of trigeminal sensitization.[63] Therefore, it is obvious that sensitization of the trigeminal system involves in the development of CM.

CM patient exhibits both cephalic and extracephalic allodynia, corresponding to respective sensitization of the second-order neurons in medullary horn or third-order thalamic neurons.[8] Central sensitization has been long accepted as a pathophysiological feature and process chronic pain conditions, manifesting as a prolonged but reversible increase in the excitability of neurons in central nociceptive pathways triggered by repeated nociceptive inputs.[63] The mechanisms underlying central sensitization include synaptic plasticity, imbalance between excitatory and inhibitory neurotransmitters (glutamate/GABA), and derangement of monoamine neurotransmitters (5-HT, norepinephrine, and dopamine).[64] In addition to neural plasticity, recent studies have implicated glia–neuron interaction in chronic pain; future studies can focus on the role of glia in migraine and its progression.[65]

Increase in cortical spreading depression-evoked Fos expression and upregulation of 5-HT_{2A} receptor in spinal trigeminal nucleus was observed in rats with chronic acetaminophen exposure.[66] Sustained morphine in rats induced lower electrical and mechanical activation thresholds in medullary dorsal horn neurons.[49] Moreover, both chronic dural inflammatory stimulation and triptan overuse caused mechanical allodynia and trigeminal sensitization in rats.[67] All these preclinical studies indicate that both frequent attacks and medication overuse promote the development of central sensitization. In addition, comorbid mood disorder also can influence the formation of hyperalgesia, as depression models induced by olfactory bulbectomy or unpredictable chronic mild stress both exhibited severer nociceptive behavior and hyperalgesia state.[68,69]

Peripheral sensitization also plays a role in development of CM. A significant increase of TRPV1 (transient receptor potential vanilloid type-1 receptor) immunoreactive nerve fibers in the arterial wall has been found in CM patients compared with control patients.[70] Expressed in small sensory neurons, TRPV1 receptors evoke release of CGRP and substance P, causing a higher sensitivity to algogenic agents. TRPV1-positive neurons can be decreased by onabotulinumtoxin A in the rat trigeminal ganglion, suggesting that TRPV1 may be a potential therapy target for CM.[71]

Molecular mechanisms

The clinical heterogeneity of migraine and the "featureless" of CM bring great diagnostic and therapeutic challenges to clinicians. And lack of appropriate biomarkers delays accurate diagnosis and impedes development of more effective therapeutic methods for migraine. Recent studies have identified several molecules which involve in the development and progression of migraine.[72]

CGRP. Peripherally secreted from trigeminal afferents, CGRP mediates vasodilation and inflammatory events within the dura as well as trigeminal ganglion, which is important in triggering and amplification of a migraine attack.[73] Significant elevations of saliva CGRP have been noted in the premonitory and headache phase of migraine compared with baseline (interictal) levels, which is predictive of responsiveness to rizatriptan.[74] Interictal increase of CGRP levels in peripheral blood has been found among CM patients compared with both EM patients and non-headache controls,[14] supporting its role as a reliable biomarker for CM. Also, the probability of being a responder to onabotulinumtoxin A was much higher for CM patients with an elevated CGRP level.[75] Moreover, TEV-48125, a monoclonal anti-CGRP antibody, has been proved to be tolerable and effective for the therapy of CM in a phase 2b clinical trial.[76] The CGRP receptors also widely express in the central nervous system and may exert pain-modulation effects;[77] future work can focus on this aspect of CGRP.

5-HT. Mainly released from the brainstem, 5-HT has long been implicated in the pathophysiology of migraine, especially in the descending pain modulation.[33] Peripherally, serotonin exerts vasoconstrictive and anti-inflammatory effects via 5-HT_{1B} and 5-HT_{1D} receptor, respectively, which is therapeutic target for triptans.[78] Besides the pain modulation, 5-HT also plays an important role in sleep pathophysiology and the genesis of mood disorders,[79] making these problems common in migraine, especially CM. According to clinical and preclinical studies, both the frequent headache attacks and medication overuse can induce decrease of 5-HT and upregulation of serotonin receptors,[67,80] which enhances hyperalgesia and promotes headache chronicity. Furthermore, abnormality of

serotonin-related metabolism is present in CM and MOH sufferes.[81,82,83]

PACAP. Recent studies have reported low levels of interictal PACAP in migraine patients,[16,84] suggesting a possible role for PACAP in the pathogenesis of migraine. Particularly, the interictal PACAP plasma levels negatively correlated with attack duration in the CM cohort.[16] In addition, decreased PACAP content in plasma and trigeminal ganglia and increased PACAP related receptor expression in the trigeminal ganglia have been found in rats after repetitive chronic dural inflammatory stimulation.[85] This decrease of PACAP induced by frequent headache attacks and the subsequent upregulation of related receptors maybe important in migraine progression and may serve as a novel target for migraine treatment. However, in another analysis of CM patients, interictal serum PACAP levels were not increased or decreased in CM women when compared to matched controls.[86] Further studies are needed to confirm the precise role of this neuropeptide in migraine and migraine chronicity, as the sample sizes are quite limited in current researches.

Others. Elevation levels of tumor necrosis factor α were found in cerebrospinal fluid of CM patients,[87] indicating the role of inflammation and endothelial dysfunction in the progression of migraine. Both CM and MOH have been associated with higher levels of cerebrospinal fluid orexin-A,[56] which maybe an expression of hypothalamic response to stress due to chronic pain. The brain-derived neurotrophic factor has also been linked to CM,[88] indicating the role of glia-neuron interaction in CM. Both CM and MOH patients have endocannabinoid system dysfunction, which may be related to serotonin system and then contribute to the chronification of both diseases.[15]

Management of CM

With confusion in the pathogenesis, CM is undertreated currently. Once the chronification is established, the treatment response becomes poorer. Therefore, in the management of CM, the first and most important step is to avoid the formation of CM by rigorous control of risk factors, including sufficient pain relief, timely prophylactic treatment of migraine, effective management of mood disorder, and other comorbidities.

Therapeutic options for CM are quite limited, and evidence-based effective treatment includes topiramate, onabotulinumtoxin A, and some neuromodulation therapy patterns. The efficacy and safety of topiramate for treatment of CM has been proved by double-blind RCTs, and a daily dose of 100 mg is generally effective and tolerable.[17] A standard injection pattern of Onabotulinumtoxin A is effective and well-tolerated for prophylaxis of headache in CM patients as shown in the PREEMPT (two phase three studies: 24-week, double-blind, placebo-controlled, parallel-group phase, followed by 32-week, open-label phase) study.[89] Some other preventive medications, including amitriptyline, valproate, gabapentin, and pregabalin, have also been shown to be effective in CM therapy in limited studies, which remains to be further investigated.[90] For pharmacologically intractable CM patients, neuromodulatory methods targeting at peripheral or central modulation may offer help through both invasive and noninvasive patterns, such as blockade of the greater occipital nerve, occipital nerve stimulation, vagal nerve stimulation, and transcranial magnetic stimulation.

In treatment of CM, the modification of comorbidities such as sleep and mood disorders is as important as pain relief. And for anxiety/depression disorder in CM patients, tricyclic antidepressants (amitriptyline) seem to be more effective than SNRIs (selective serotonin/norepinephrine reuptake inhibitor) and SSRIs (selective serotonin reuptake inhibitor),[91] but large-scale clinical trials are needed to verify the best option.

Summary

Transformed from EM, CM is featured by higher headache frequency, lager ratio of comorbidities, and severer disease burden. Some risk factors associated with migraine transformation have been identified, of which medication overuse, insufficient pain relief, and mood disorders need to be concerned in the attempt to avoid migraine chronification. The pathophysiology of CM is not fully understood, and recent advances in electrophysiology and neuroimaging have indicated that cortical hyperexcitability, brainstem dysfunction, and central sensitization are important in the development of CM. Taken together, CM may differ from EM in central excitability which links to headache progression toward a nearly daily basis. Alterations in much brain regions have been identified in CM patients, but future longitudinal studies are required to determine whether these plastic changes are causes or consequences of migraine chronification and whether they can serve as a "brain signature" for migraine phenotypes, evolution, and prognosis. Several molecules have also been identified in CM patients by biochemical analysis, which may serve as biomarkers of CM and also potential therapeutic targets. For management of CM, rigorous control of risk factors is most important, and the most established preventive therapies for CM include topiramate, onabotulinumtoxin A injections, and some neuromodulatory methods.

Declaration of Conflicting Interests

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