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EPISODIC MIGRAINE (S. NAHAS, SECTION EDITOR)

Episodic Migraine Comorbidities: Avoiding Pitfalls and Taking Therapeutic Opportunities

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Abstract

Migraine is a common neurologic disorder. This article will discuss a few factors that influence migraine (mostly episodic) and its treatment, such as sleep, obstructive sleep apnea (OSA), obesity, and affective disorders, as well as autoimmune diseases. Practitioners must be aware of these coexisting conditions (comorbidities) as they affect treatment. It is noted in literature that both the quantity (too much or too few hours) and the quality (OSA related) of sleep may worsen migraine frequency. An associated risk factor for OSA, obesity also increases migraine frequency in episodic migraine cases. A bidirectional relationship with migraine along with depression and anxiety is debated in the literature. Retrospective cohort studies are undecided and lack statistical significance, but prospective studies do show promising results on treatment of anxiety and depression as a means of improving migraine control. Finally, we address the topic of autoimmune diseases and migraine. While few studies exist at this time, there are cohort study groups looking into the association between rheumatoid arthritis, hypothyroidism, and antiphospholipid antibody. There is also evidence for the link between migraine and vascular diseases, including coronary and cerebral diseases. We suggest that these comorbid conditions be taken into account and individualized for each patient along with their pharmaceutical regimen. Physicians should seek a multifactorial treatment plan including diet, exercise, and healthy living to reduce migraine frequency.

Keywords Migraine · Sleep · Anxiety · Depression · Obesity

Introduction

Migraine is a common neurological disorder divided into either episodic or chronic, based on its frequency. Episodic migraine is the term when the number of migraines is less than 15 days a month [1••]. A number of studies look at the comorbidities that are associated with migraine, or other diseases that are more likely to be present in those with migraine than in those who do not have migraine. Although, there are some differences between the associated comorbidities in chronic and episodic migraine, there is also some overlap.

The Chronic Migraine Epidemiology and Outcomes (CaMEO) study, one of the larger migraine studies, is a cross-sectional and longitudinal study that addresses the associated conditions related to both episodic and chronic migraine [2••]. The study included approximately 15,000 people, of whom 91% were classified as having episodic migraine. According to CaMEO, 28% of participants with episodic migraine also had generalized anxiety disorder, while 30% screened positive for depression. Those with episodic migraine were also more likely to have a full-time job compared with those with chronic migraine, as well as a higher educational status [2••]. Here, we attempt to look at a collection of common comorbidities associated with episodic migraine, how they relate, affect disease course, and may be treated together.

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Migraine and Sleep

There is a large body of literature regarding the role of sleep in migraine, but the relationship still remains poorly defined. Undersleeping and oversleeping have been described as precipitants for migraine. Those with migraine often have used sleep or naps to abort an attack [3]. Sleep disorders come in a multitude of flavors and need to be considered when discussing migraine management with patients as it appears to be involved in onset and resolution of symptoms.

Quality, quantity, and sleep patterns all play a role in migraine. In a study of 1283 patients with migraine, lack of sleep was reported as a trigger in 50% of patients and oversleeping was reported as a trigger in 37% of patients. Sleep is a migraine alleviator or abortive for 85% of those studied [4]. Migraine may commonly occur during sleep, result in nighttime awakenings, and lead to disrupted sleep patterns. A study of 1698 patients with migraine found that almost half of the patients' migraine attacks occurred between 4 am and 9 am, suggesting that migraine occurs during REM sleep stages [5]. The pathophysiology of this relationship is proposed to involve the hypothalamus, serotonin, and melatonin, but the exact mechanism is not yet defined [6].

Fatigue is a common complaint among those with migraine and it is imperative for physicians to discuss sleep habits with patients. In a case-control study by Barbanti and colleagues, excessive daytime sleepiness was reported more frequently in patients with episodic migraine compared to control [7]. This excessive daytime sleepiness was associated with increased migraine disability, higher anxiety level scores, and more frequent reports of sleeping problems (i.e., sleep quality and efficiency) [7]. The daytime sleepiness and fatigue, then, likely reflect poor nighttime sleep, which seems to contribute to worsening headache symptoms. Eliciting a history of excessive sleepiness during the daytime or snoring may help identify an underlying sleep disorder, which may require a sleep specialist for treatment assistance as many headache patients suffer from insomnia and sleep apnea. In 2010, Sancisi and colleagues assessed sleep patterns in 105 patients with chronic headache. Over two thirds suffered from insomnia, with nearly half of these patients reporting snoring during sleep [8]. This higher prevalence compared with controls suggests that sleep disorders may be a risk factor for headache chronification [8]. In the previously aforementioned study by Kelman and Rains, almost half of the patients reported difficulty initiating and maintaining sleep, with frequent nocturnal awakenings [4]. Of the participants, 38% reported sleeping an average of 6 h a night, a sleeping pattern similar to those with insomnia. These short sleepers were found to have more severe and more frequent headaches when compared with those who slept longer (more than 6 h a night) [4]. Sleep modification with melatonin or amitriptyline (a known migraine preventive with the side effect of drowsiness) may help these patients. When studying obstructive sleep apnea (OSA) and migraine, Johnson and colleagues found a strong relationship with OSA and the migraine types, 50% in episodic and 83% in chronic [9]. This was a retrospective review of patients diagnosed with polysomnography testing. Of these patients with obstructive sleep apnea, 76% reported frequent snoring, 69% frequent nocturnal awakenings, 61% recurring morning headaches, and 62% repetitive fatigue [9]. When treated with continuous positive airway pressure (CPAP), reduction in headache severity and frequency occurred in 33% of episodic migraine patients and 50% of chronic migraine patients (a 50% reduction) [9]. Of all patients included in the study, 78% reported improvement when adherent to CPAP [9]. CPAP, therefore, may be a useful treatment for migraine patients who also report snoring, fatigue, or frequent nighttime awakenings.

Sleep disturbances are well known among those with headaches, with a higher prevalence in patients with chronic daily headache, awakening headache, or morning headache. This serves as a unique opportunity for physicians, both diagnostically and therapeutically. The range of sleep disorders prevalent in those with migraine varies widely. In a randomized controlled trial of chronic migraine patients, sleep behavioral modification therapy was shown to help patients revert from chronic migraine to episodic migraine [10]. In these patients, the number of sleep behavior changes was directly proportional to the improvement in headache intensity and frequency, further solidifying the relationship between sleep hygiene and headache syndromes [10]. Eliciting this history early and counseling on aberrant sleep behaviors, or referrals to sleep specialists, may alter headache course, decrease future disability, and improve quality of life [11].

Restless legs syndrome (RLS), which involves an unpleasant sensation in the legs worse at night and resolved by movement, is more prevalent in patients with migraine than those without migraine. Rates of RLS in patients with migraine have been reported to range from 8 to 39%, and studies have shown that the severity of RLS correlates with increased headache frequency in migraine [12–14]. The proposed pathophysiology of the relationship between RLS and migraine involves dysfunction of central dopaminergic pathways, or imbalance of dopaminergic activity [15]. Dopamine has been implicated in premonitory symptoms in migraine such as yawning, gastrointestinal disturbances, and food cravings, and patients with migraine who also have RLS report premonitory symptoms more frequently than those without RLS [16]. RLS also seems to be an independent predictor of poorer quality sleep, which may also then predict worsening headache frequency and transformation to chronic migraine [15]. One potential treatment for patients with migraine who have RLS may be dopaminergic agents such as ropinirole and pramipexole, which may improve RLS symptoms, thereby aiding in improving sleep for these patients which may subsequently improve migraine frequency.

Migraine and Obesity

Migraine, whether episodic or chronic, is comorbid with obesity. According to the World Health Organization, obesity is classified as having a total body fat percentage greater than 35% in woman and greater than 25% in men. General obesity based on BMI is estimated as a BMI of greater than or equal to 30 kg/m^2 [17]. The link between migraine and obesity has been well documented with more than a dozen studies conducted on patients of all ages and types. A majority of general population studies have shown a significant association between obesity and migraine in reproductive-aged individuals (mean age less than 50) and no association in those of perireproductive or post-reproductive age [18].

The evidence indicates that obesity raises the risk of having migraine as much as 50%. The risk of migraine increases with increasing obesity status—from normal weight to overweight to obese. In a cross-sectional study by Vo et al., the risk of migraine in reproductive-aged women substantially increased with increasing severity of obesity. The overall odds of migraine in women with obesity of any level were 48% greater than those without obesity. However, those with severe obesity (BMI 35–39.9) had an over 200% increased risk. And those with morbid obesity (BMI ≥ 40) had a 275% increased risk of migraine [19]. Obesity also increases the risk of someone with an episodic pattern of headaches transforming to a chronic pattern. In a cross-sectional analysis of more than 30,000 participants, Bigal and Lipton found that the risk of chronic migraine was increased by 50% in those with BMI between 30 and 34.9 and by 100% in those with BMI greater than35 compared with those of normal weight [20].

There are several potential mechanisms for the migraine–obesity relationship. Peripherally, weight gain leads to expansion of adipose tissue triggering the recruitment of macrophages and T cells. In addition, there are changes in the synthesis of cytokines and adipocytokines by adipocytes that favor chronic systemic inflammation and insulin resistance. Weight gain is known to lead to the induction of pro-inflammatory cytokines including, but not limited to, tumor necrosis factor alpha, interleukin-1, and other interleukins. Elevated plasma concentration of these pro-inflammatory cytokines and alterations in adipocytokines have been implicated in the pathogenesis of migraine [18]. Centrally, the hypothalamus regulates feeding and is activated during migraine attacks. Functional imaging data has confirmed hypothalamic activation during migraine attacks and demonstrates that several hypothalamic peptides, proteins, and neurotransmitters involved in feeding (serotonin, adiponectin, leptin, and orexin) are implicated in migraine pathophysiology [18].

As obesity is a potentially modifiable risk factor, migraine patients and clinicians treating patients with migraine should be aware of this association and consider each individual's obesity status in regard to both lifestyle education and medication choices. Patients should be provided with access to lifestyle education, particularly in regard to diet and exercise routines. Lack of physical exercise is associated with a 21% increased risk of headache attacks in adult migraine patients and a 50% increased risk of migraine in adolescents [21]. Aerobic exercise may reduce headache frequency in those with episodic migraine [22]. Preventative medications for migraine in obese patients should be chosen carefully. Those associated with weight loss include topiramate, zonisamide, and protriptyline. Other potential agents where weight loss is mild or neutral include timolol, candesartan, venlafaxine, and duloxetine [23].

Despite mechanisms linking migraine to obesity, few studies have examined the impact of weight loss on migraine in obese adults. There have been two small clinical studies evaluating change in headache frequency after weight loss from bariatric surgery. In these studies, the monthly headache frequency dropped from approximately four headache days per month to just one to two headache days per month at 6 months post-operation. While these studies suggest that weight loss is associated with a decline in headache frequency, larger controlled trials are needed to substantiate these findings before bariatric surgery can be considered as part of migraine therapy [24].

In summary, migraine is associated with obesity in those of reproductive age. Clinicians are urged to educate all migraine patients on the association of migraine with obesity and the potential effect of weight gain and weight loss on headache frequency.

Migraine and Affective Disorders

Affective disorders are comorbid among individuals with migraine [25]. There appears to be a bidirectional relationship between depression and/or anxiety and migraine, which may increase disease burden and influence outcomes [26]. There are multiple population-based control studies that have linked migraine with anxiety and depression. When comparing pain and migraine within the general population, anxiety disorders are "two to ten times more prevalent in migraineurs than in the general population" [27]. Patients may suffer from anxiety regarding their pain and develop habits such as patterns of avoidance. This can provoke symptoms and feed into one another, as one fears the next headache and may become socially avoidant [28]. Pain and avoidant habits may be why there is an increased 12-month risk of self-harm or suicide, especially for migraine with aura, even when adjusted for age, sex, and history of affective disorders like anxiety. While Novic and team point out that there was no correction for pain intensity, they quote Ilgen et al. in stating that suicide risk is greatest in those with migraine when compared with other

conditions such as arthritis, back pain, headache, or fibromyalgia [29].

There are theories as to the underlying pathophysiology that links migraine and affective disorders. Pain perception may be altered by nociceptive signaling in the descending pain pathway and sensitization of the trigeminovascular pathway, which results in an excitatory–inhibitory imbalance [25]. These pathways project from the periaqueductal gray to the brainstem via serotonergic neurons in the medulla and noradrenergic neurons in the pons and tegmentum. Each successive migraine may further decrease the concentration of serotonin thereby lowering pain thresholds and prompting recurrent attacks. This is a possible explanation to reduced levels of serotonin found in those with migraine both during and between attacks. It also exemplifies the relationship between migraine and depression (both serotonin-deficient states). Additional links have been made to dopamine–noradrenalin imbalance from abnormal tyrosine metabolism, hypothalamic-pituitary-adrenal axis dysregulation, and NcoI polymorphism in the DRD2 gene, relating depression and migraine [25, 26, 30, 31]. Studies involving PTSD and migraine find similarities in changes between cortisol production in the hypothalamic pituitary adrenal axis and estrogen levels in child abuse victims and migraine [32]. All of which can explain the benefit from selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants for migraine patients [28].

A few more recent studies found mixed results when delving into the relationship between migraine (episodic and chronic), anxiety, and pain. A 2016 study by Palacios-Cena evaluated 155 women characterized by episodic migraine, chronic migraine, and normal controls. Over multiple locations, their pain thresholds were evaluated in a blinded study with hospital anxiety and depression scales to assess clinical features of anxiety, depression, and migraine. No difference was seen between episodic and chronic migraine ($P > 0.919$). There also was no difference when comparing migraine with anxiety ($P > 0.425$) and depression ($P > 0.316$). This is similar to the cross-sectional study by Mosheni et al., which did not find significant differences. These groups both recognized confounding factors to influence their study results, i.e., degree of participants' anxiety and concordant antidepressant use [33–34]. However, another cross-sectional study did find that anxiety was significantly greater with chronic migraine than the episodic form of migraine, as well as with those with medication overuse headache, though not significant. Number of headache days shared a positive relationship with psychosocial worsening in the episodic migraine type, but eventually leveled off around 15 headache days per month (13.3 days with statistical analysis) [35].

While the literature may appear undecided on the degree to which episodic and chronic migraine correlate to different forms of affective disorders, it is clear that they do coexist. Clinicians must be aware of this and screening patients for these comorbidities can help with treatment. Compliance may be improved by easier regimens, which treat two conditions with one medication, and lead to better outcomes when treating the patient as a whole. It must be noted, though, that in severe cases, each condition may require different doses for effective management. Treatment of migraine may also negatively affect comorbid conditions, such as bipolar disorder, requiring clinicians to be well versed in psychological diseases and treatment options. Migraine may occur in approximately 30.4% of bipolar patients (ranging from 15.7 to 58%) or at 12–13% of the rate of migraine in the general population. In psychiatric clinics, it is noted that migraine commonly occurred in patients with major depressive disorder and bipolar disorder [36]. Medications, especially serotonin–norepinephrine reuptake inhibitors and tricyclic antidepressants, can cause bipolar patients to convert into manic, hypomanic, or rapid cycling states. Providers must be careful as, according to Leo and Singh, those with migraine are more likely to convert to manic states with antidepressants when compared with those without migraine. In this case, a headache specialist may consider anticonvulsants (i.e., topiramate), atypical antipsychotics (i.e., olanzapine or quetiapine), and the calcium channel blocker, verapamil [36]. Migraine specialists should also work with psychiatrists and psychologists for non-medicinal headache management ideas. In a VA-based study, veterans with migraine were screened by Patient Health Questionairre-8 or Generalized Anxiety Disorder Scale-7 and incorporated into ACT plus Migraine Education workshops of 4–6 members. Veterans reported increased ability to manage stress, migraine, better mood, and self-awareness. Participants also appeared more comfortable approaching their providers to discuss medication management [37]. Combining medication with cognitive behavior therapy, acceptance and commitment therapy (ACT), illness education, and lifestyle modifications may all benefit these patients and comorbidities.

Migraine and Autoimmune Diseases

There are few studies to clarify whether a relationship exists between autoimmune diseases and migraine. Some studies suggest comorbidity between specific autoimmune diseases and migraine.

Rheumatoid arthritis (RA) and thyroid disease have been reviewed in relation to migraine. One of these studies looked at whether patients who had migraine were more likely to later develop rheumatoid arthritis. Nearly 58,000 patients with a diagnosis of migraine were compared with a similar number of age and sex-matched control group. In the follow-up, there was a near twofold increase in the development of RA in those patients with migraine [38]. Another longitudinal,

retrospective cohort study assessed migraine and thyroid disease. Participants were followed at a 3-year interval for a total of 20 years. At every visit, participants were asked about a headache diagnosis and screened for thyroid disease. There were over 8000 participants and there was a slight association between diagnosis of any headache disorder and hypothyroidism, with a hazard ratio of 1.21 (95% CI 1.001, 1.462) [39]. Another study evaluated the association of subclinical hypothyroidism and migraine in children. They evaluated 98 children, but there was no significant association between subclinical hypothyroidism and children with migraine. They did not feel that it was necessary to screen children who are diagnosed with migraine to be screened for hypothyroidism [40].

A comorbid association between migraine and antiphospholipid abnormalities may exist. In 2017, there was a systematic review and meta-analysis conducted to evaluate this association. There were 13 articles selected evaluating a total of 912 participants with migraine compared with healthy controls. A significant association of those with migraine and the presence of anti-cardiolipin antibody as well as anti-beta2-glycoprotein antibody was found. Lupus anticoagulant did not have the same significant association [41]. This may lead some credence to the theory that migraine is an autoimmune-associated disorder.

Autoimmune diseases and migraine is another relationship that is deserving of further research. Thus far, rheumatoid arthritis, thyroid disease, and antiphospholipid abnormalities have been incompletely assessed.

Migraine and Vascular Disorders

There is a growing body of evidence for the link between migraine and vascular diseases. There is a known well-established link between migraine and stroke, more strongly linked with migraine with aura. Migraine is associated with almost a two times increased risk of ischemic stroke [42]. A prospective study by Kurth in 2016 examined the link with cardiovascular disease and found that women with migraine had an elevated risk of myocardial infarction, angina, and cardiovascular mortality [43]. In those who have a history of cardiovascular disease, treatment for their migraine should be considered carefully. It is important to make sure that other clear risk factors are well controlled, including hypertension and smoking. In these patients, the use of triptans is controversial as there is fear for constriction of blood vessels. Non-steroidal anti-inflammatory drugs (NSAIDs) also carry a black box label for the association with increased risk of heart attack.

When possible, other abortives such as metoclopramide, prochloperazine, diphenhydramine, baclofen, acetaminophen, and gabapentin are good options and do not carry a known risk of vessel constriction. Trigger point injections and nerve blocks are other good options. The use of preventives in these patients also requires consideration of their other risk factors. Beta blockers and ace-inhibitors may be good options in patients who may also have hypertension, for the use of preventive therapy.

Raynaud's phenomenon which is a condition associated with cold hands and feet which can also change color and may be painful. It is caused by constriction of arteries, particularly in the cold. There is some evidence that this condition is increased in migraine. A study in 1993 revealed that the prevalence of migraine with increased significantly in those with Raynaud's phenomenon compared with a control group [44]. Beta-blockers should be avoided in patients with Raynaud's phenomenon, when choosing a preventive, as it may exacerbate this condition; along with other medications that may increase constriction, including triptans or dihydroergotamines.

Migraine and IBS

Migraine is also intertwined with irritable bowel syndrome. Shared traits include their characteristic chronic pain without known organic causes, objective diagnostic criteria, and triggers [45]. Young females may be prone to both of these conditions and appear to be more likely to suffer from both diseases than the risk for each separate disease in the general population.

The increased frequency between the two is supported by literature. In a retrospective cohort study, migraine patients without IBS were followed along with control subjects with neither condition. These patients were observed for diagnosis of IBS. It appeared that the cohort arm with migraine were more likely to develop IBS, a 2.45-fold higher cumulative incidence. This increased risk was maintained among males and females [45]. A study population in Sweden looked at those with irritable bowel syndrome and found that migraine was a comorbid condition in 40% of the female and 28% of males [46]. The HEAD-hunt study in Norway had similar findings among 51,000 study participants [47]. A relationship has clearly been defined, but the why remains unanswered.

There are multiple theories to explain the possible relationship between the two diseases. One theory is hyperexcitability of the nervous systems in susceptible patients. Increased activation of parts of the brain, such as that exhibited on fMRI in the hypothalamus, thalamus, and brainstem, can result in abnormal central pain processing. In fact, fMRI studies of IBS patients show similar changes in cerebral gray and white matter. Serotonin, which also exists in the gut, may be the link between migraine, pain sensitization, and communication with the gastrointestinal tract [45]. The brain–gut axis may also result in neuroimmune reactions [47]. The gut microbiota and its effect on brain functions and disease is of recent interest in many neurologic diseases, including migraine. Food allergy antigens may produce IgG antibodies and cytokines that result in inflammation and are proposed to increase migraines. The gut mucosa of irritable bowel syndrome patients has more mast cells than healthy intestines. These patients have a defect in gut

permeability and are more sensitive to dietary antigens on the lamina propria, which results in greater IgG antibody production. There is a range of food categories that may have these immunoglobulins, i.e., seeds, gluten, and eggs [48]. A hereditary, genetic polymorphism, or biopsychosocial relationship needs further exploring as well [49].

Medical and dietary treatment options exist for those patients suffering from both conditions. Serotonin (5HT) agonists and antagonists affect gastrointestinal motility and visceral hypersensitivity. It is also important in migraine attacks, which are treated by triptans ($5HT_{1D}$agonists). Long-term use of antidepressants like tricyclics may benefit both diseases [45]. IgG elimination diets have shown significant reduction in migraine attacks and irritable bowel-related symptoms. Patients should be tested for serum IgG antibody titers and items should be eliminated on an individualized basis. There may not be a specific "migraine diet," but rather specific foods that act as triggers for patients [48]. Probiotics may also be considered but needs further studies [47].

Conclusions

Migraine is a complicated disease that affects many people. While we do not yet fully understand what causes migraine or how to treat it, it is clear that a patient's migraine course is affected by numerous internal and external factors. The patient and physician should not become frustrated and instead should work together and listen to one another to create a multimodal approach for the patient to achieve the best outcomes.

Compliance with Ethical Standards

Conflict of Interest Britany Klenofsky, Anna Pace, Lauren Natbony, and Huma U. Sheikh declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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