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REVIEW

Sleep Symptoms in Migraine

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Abstract

Purpose of Review To review replicated and highlight novel studies of sleep in children and adults with episodic and chronic migraine.

Recent Findings Attack-related sleep symptoms are most common in the prodrome and may represent early activation of the hypothalamus rather than migraine triggers. Interictally, patients with migraine report poor sleep quality and high rates of insomnia symptoms. Cognitive behavioral therapy for insomnia in adults and adolescents with chronic migraine and comorbid insomnia results in significant improvement on their headache burden. Thus far, objective studies report that migraine per se is a not associated with sleep apnea. At the present time, there is minimal evidence that migraine is under circadian influence.

Summary The current body of evidence suggests that the insomnia symptoms and poor sleep quality commonly reported by patients with migraine are not attack-related but occur interictally and are a marker of worsening disease. The development of clinical guidelines to approach sleep symptoms and expansion of CBT-I trials in those with episodic migraine would be clinically valuable.

Keywords Sleep Symptoms · Migraine · Insomnia · Sleep Quality

Introduction

Patients with migraine commonly report sleep symptoms, both during attacks and interictally. Clinicians have historically advised patients on sleep routines and in some cases, attempted to treat attacks with sedating medications [1, 2]. Research studies have confirmed and attempted to characterize the high rates of sleep symptoms and disorders in adults and children with migraine. More recently, studies on sleep and migraine have utilized prospective design, validated objective and subjective measures of sleep and well-recognized diagnostic criteria of migraine. This has allowed for further insight into the complex multi-faceted relationships encountered clinically. We review replicated and highlight novel studies on sleep across a migraine attack and at baseline (interictally, between those with and without migraine) in children and adults with episodic and chronic migraine.

Migraine Background

Migraine is a lifelong neurologic illness defined by recurrent attacks of moderate or severe headache, photophobia and nausea lasting 4–72 h [3]. Approximately one-third of those with migraine experience an aura prior to headache onset, lasting up to one hour and characterized by transient neurologic disturbances, most commonly visual obscurations. In the hours or day prior to headache, some patients identify prodromal symptoms which include changes in sleep, mood or appetite [4]. Upon resolution of headache pain, patients experience a one-day postdrome, with tiredness/weariness reported in 88% of prospectively captured attacks [5]. Additionally, migraine attacks are associated with transient changes in emotional state, cognitive abilities, dizziness, GI disturbance and other symptoms which vary between individuals and episodes. Historically, those with migraine have been thought to have a higher susceptibility

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to certain life-long characteristics, such as motion sickness which afflicts about 2/3 of those with migraine [6]. Migraine is also highly comorbid with mental and medical disorders including anxiety and depression, GERD and asthma/allergies. A diagnosis of migraine with aura carries a two-fold increased risk of stroke, although the exact mechanism is still debated [7]. Despite many decades of investigations for biomarkers (EEG, serum, and CSF testing), and strong evidence for genetic predisposition, common migraine remains purely a clinical diagnosis [8].

Globally, migraine has a population prevalence of 14% and is ranked as the 3rd most disabling disease in those under 50 [9]. It is twice as common in women as men and is most active during early/middle age [10]. Chronic migraine is a more severe subtype which affects 1–2% of the general population and is defined as having fifteen headache days per month over the last 3 months [3, 11]. In clinical practice, and in epidemiologic studies, adults and children with chronic migraine report high rates of comorbidities (anxiety/depression, chronic pain conditions, respiratory, and cardiovascular risk factors), and experience worse disability and a more refractory treatment course than those with episodic migraine [12]. Migraine is commonly encountered clinically and is the most common diagnosis in outpatient neurology visits [13]. The natural history of the disease often results in a long-term therapeutic alliance, with attention to and management of comorbidities including sleep complaints.

Sleep Symptoms across the Migraine Attack

Patient-reported sleep symptoms and objective changes in sleep parameters have been reported across the phases of a migraine attack (see Fig. 1). Along with stress, changes in sleep quality and duration are the most commonly reported migraine attack trigger [14]. However, as with other purported triggers, prospective studies reveal a much weaker association (if any) than retrospective studies. Three studies have prospectively tracked sleep and headaches in those with episodic migraine using electronic diaries and actigraphy, a non-invasive validated method of measuring sleep parameters using a wearable accelerometer. Collectively, they report no changes in actigraphy-measured sleep duration and latency the night before or after a headache attack in adults and children with episodic migraine [15–18]. One study which followed one hundred adults with episodic migraine over six weeks reported lower sleep efficiency

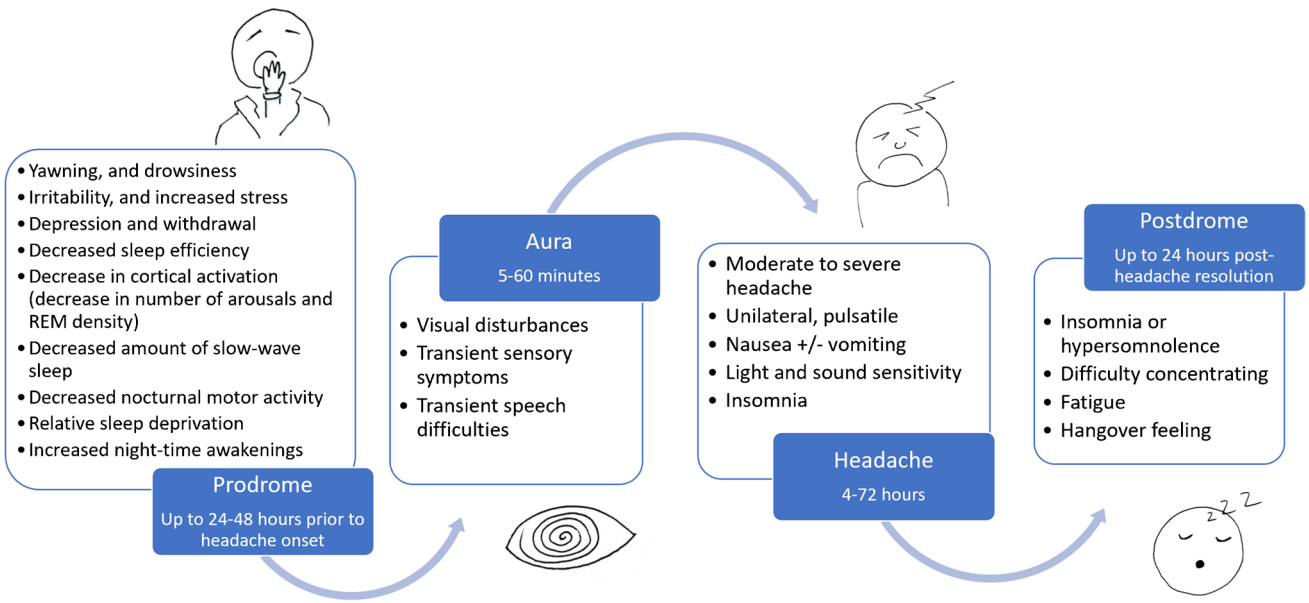

Fig. 1 Sleep and energy related symptoms over the course of a migraine attack. Legend: A migraine attack may include four phases: prodrome, aura, headache, and postdrome. Prodromal symptoms occur in the hours (in some, up to 48 h) before headache onset, and can include sleep and mood changes, yawning, irritability, depression, and withdrawal [4]. Patients report relative sleep deprivation and increased nighttime awakenings prior to migraine attacks, with limited PSG studies reporting decreased cortical activation (i.e., decrease in REM density and nocturnal motor activity) and actigraphy studies reporting decreased sleep efficiency two nights prior to a headache attack [16, 18, 20]. The hypothalamus has been shown to be active in the prodrome on imaging studies [21]. Aura, experienced by 1/3 of patients, precedes the headache by up to 60 min, and most often presents as visual disturbances or transient focal neurological symptoms, without associated sleep symptoms. The headache phase is characterized by moderate to severe head pain, nausea, photophobia and phonophobia. Insomnia has been retrospectively reported by patients during this phase, but not confirmed in prospective diary or actigraphy studies [15, 16, 18]. The postdrome is most commonly described as a fatigue or hangover feeling, although some patients report insomnia or hypersomnolence [5].

two nights prior to a migraine attack, suggesting that sleep changes may start earlier [16••]. Inherently challenging older polysomnography (PSG) studies in patients with episodic migraine reported increased awakenings and decreased amounts of slow wave sleep in the nights before an attack in those with sleep related attacks or morning attacks, without clear differences in sleep latency or total sleep time [19, 20].

With respect to sleep quality, two studies reported no intraindividual changes in sleep quality the night before or after a migraine attack [16, 22]. The most recent study conducted in adults and children reported that worse sleep quality was associated with morning but not afternoon onset headaches, and that morning onset headaches may be more representative of a migraine phenotype rather than a tension-type headache phenotype [15]. Further studies are needed to replicate this interesting finding.

In addition to sleep, perceived stress is also a reported immediate precedent to headache days in those with episodic migraine [23]. In those with chronic migraine, stress may interact with poor sleep to confer migraine risk two days later [24]. These studies suggest that decreased sleep efficiency may precede headache by several days, sleep symptoms prior to an attack may differ by migraine subtype (episodic vs. chronic) and may be related to stress. The timing of these findings, together with imaging evidence of migraine attack progression, suggest that changes in sleep parameters prior to a headache may be secondary to hypothalamic activation during the prodrome [25, 26].

Use of Sleep as an Abortive Treatment

Clinicians historically observed that patients who slept during a migraine attack had faster resolution than those who did not [2]. As such, sedating medications or naps were encouraged as an adjunctive analgesic strategy in acute settings [2, 27]. In observational studies, use of napping is especially common in children under 8 years old (during 60% of attacks) and is less common in adolescence and adulthood [28]. The rates of daytime napping in adults with episodic migraine are similar to napping rates in the general US population (approximately one nap/week) [29]. In US working-age adults with episodic migraine, there is an increased risk of napping on day 2 of a headache compared to a non-headache day, without appreciable impact on subsequent actigraph-measured nighttime sleep [17]. Therefore, if feasible and preferred by the patient, a shorter daytime nap (< 1 h) may be a low-risk adjunct migraine treatment strategy. Of note, napping recommendations may differ in patients with chronic migraine who may tend to take longer naps and be at higher risk for the development of abnormal sleep patterns or disorders [30].

Sleep Symptoms Baseline (Interictally)

Self-reported Sleep

Adults and children with episodic migraine consistently report worse sleep quality compared to those without migraine on standardized questionnaires, of which the Pittsburgh Sleep Quality Index (PSQI) has been the most utilized [31–38]. Poor sleep quality is also associated with headache frequency and severity. In prospective analyses, poor quality sleep at baseline was predictive of higher headache frequency over the following six weeks in adults with episodic migraine [39]. In patients with chronic migraine, poor sleep quality is associated with worse headache severity [24, 40]. Together, studies suggest that patient report of poor sleep quality is associated with migraine disease severity and may be a marker of disease progression (converting from episodic to chronic migraine).

In addition to sleep quality, those with migraine report higher rates of subjective sleep symptoms. Sleep disturbances of any type are more commonly reported in those with chronic rather than episodic migraine [31, 41–43] and in those with high rather than low frequency episodic migraine [44]. In those with episodic migraine, self-reported short sleep duration has been associated with worse headache frequency [37, 45]. Worse multi-dimensional sleep health scores (a combination of sleep quality, duration, regularity, alertness, timing and satisfaction) were associated with 3–4 more headache days per month in adults with episodic migraine in prospective studies with actigraphy and daily diaries [46]. Longer duration longitudinal studies may provide insight into the now well-established cross-sectional associations of migraine and poor sleep quality and further characterize other self-reported sleep complaints [47••].

Objectively Measured Sleep

Polysomnographic studies (PSG) of patients with episodic migraine have been limited by design heterogeneity and small samples [19, 20, 35, 48–50]. Most recently, a meta-analysis examining PSG studies in adults and children reported a modestly lower percentage of REM sleep in those with migraine versus controls in both adults and children [47••]. However, the isolated finding of lower REM sleep in adults with migraine is difficult to interpret given varying frequency of migraine and inclusion of patients across many life decades over which the percentage of REM sleep is expected to change. The more robust differences in the PSG of pediatric migraine patients (less total sleep time, more time awake at night, and shorter sleep latency) in addition to lower percentage of REM sleep is more convincing of a poor sleep endophenotype [47••].

Comorbid Sleep Disorders

The comorbidity of migraine with sleep disorders has been previously reviewed [51, 52]. Here, we highlight recent and replicated findings.

Insomnia

Insomnia was the number one self-reported comorbidity associated with migraine in the US general population [53••]. In clinical and population-based samples, adults and children with episodic migraine consistently report increased difficulty falling and staying asleep compared to those without migraine on standardized questionnaires [20, 31–38, 54]. Two thirds of adults with chronic headache (including chronic migraine, chronic tension type headache, and medication overuse headache) from specialized care clinics meet International Classification for Sleep Disorders (ICSD) criteria for co-occurring insomnia [55]. Rates of chronic insomnia for those with episodic migraine are not known but expected to be lower.

Several studies have previously examined whether anxiety and depression may explain the association between insomnia symptoms and migraine, given these mood disorders are comorbid with both. Consistently, analyses have shown that controlling for these mood comorbidities do not substantively change the association between insomnia symptoms and migraine [38, 41, 56]. This suggests a possible common shared pathophysiology.

In clinical settings, insomnia is underrecognized and undertreated in patients with migraine [34]. Delayed treatment of insomnia may result in worse prognosis but may also impact migraine [57]. Interventional studies of cognitive behavioral therapy for insomnia (CBT-I) in adults and adolescents with comorbid chronic migraine and chronic insomnia, showed significant reduction in headache frequency and improvement in sleep [58–60]. Larger interventional studies in episodic migraine populations are needed, as well as guidelines for clinicians treating migraine encountering insomnia symptoms.

Obstructive Sleep Apnea (OSA)

Whether migraine is a risk factor for sleep apnea is of clinical interest, given that morning headaches are a symptom of untreated sleep apnea [3]. One-third of adults with migraine in the general population are at higher risk for sleep apnea based on the Berlin questionnaire [51, 61]. However, in-laboratory PSG studies of patients with migraine in Norway [61] as well as home sleep studies from the Hispanic Community Health Study/Study of Latinos in the US reported similar rates of OSA in adults with episodic migraine and controls [62]. This apparent discrepancy may be due to the use of a screener vs. objective testing. However, it may also be influenced by individual patient risk profile. For example, in the Berlin questionnaire study of those with migraine, rates of "high risk" of sleep apnea were 12% when considering women of normal weight alone and 79% for men with BMI > 30 [41]. Taken together, our impression is that there may be a subset of patients with migraine at higher risk for OSA (such as those with comorbid obesity), but that migraine per se is not likely to be a risk factor for sleep apnea.

Sleep-related Bruxism

Bruxism and temporomandibular joint dysfunction (TMD) are frequent clinical observations in those with episodic headaches [63]. The association with migraine is less clear as most studies of sleep-related bruxism have not phenotyped headache according to ICHD criteria [64]. Two studies in adults with episodic migraine reported a two-fold increased odds of awake and sleep bruxism [65, 66]. Small randomized controlled clinical trials of the migraine preventive medications amitriptyline and propranolol did not improve bruxism symptoms in those with sleep related bruxism (without migraine) and onabotulinum toxin-A trials (FDA approved for chronic migraine) have had modest results on bruxism [67–69].

Restless legs Syndrome (RLS)

Meta-analyses have reported a robust association between migraine and restless legs syndrome (RLS). The prevalence of RLS in migraine clinical samples is 16–19%, which is approximately twice that of non-migraine populations [70–72]. Both disorders may involve dysfunction in dopaminergic pathways, as evidenced by imaging and genetic studies [73, 74]. As such, certain medications used for migraine management (i.e., antidopaminergic antinausea medications, antihistamines, and medications that increase serotonin) may exacerbate RLS in those with migraine [75].

Circadian Rhythms and Migraine

Long-held clinical observations and newer imaging evidence across a migraine attack implicating the hypothalamus as the biological driver of migraine have spurred interest in investigating potential circadian patterns and markers of circadian activity in those with migraine [26••].

Circadian Rhythm Patterns and Migraine

Several studies have investigated the association between migraine and circadian rhythm patterns. A circannual or diurnal pattern of attacks is reported by half of those with

migraine [76]. In prospective studies, monthly incidence of attacks shows a mild broad peak between April and October [76]. In contrast, emergency room visits for migraine are reportedly higher in January and internet searches for migraine are highest in February, October, and November [77, 78]. Monthly incidence of migraine attacks may be influenced by many geographic and individual factors including annual changes in work or family responsibilities (including timing of school seasons) and weather patterns.

With respect to diurnal rhythmicity, migraine attacks are less likely to have onset during nighttime hours (23:00 to 7:00 AM) than daytime hours, in contrast to cluster headache which characteristically present during nighttime hours [76]. Clinically, there are subgroups of migraine patients who report severe attacks arising out of sleep [31, 32, 79, 80]. Nighttime migraine attack frequency increases with age, such that sixty-year-old adults report that over half of their migraine attacks arise out of sleep, compared to twenty-year-old individuals who report only one of six migraine attacks arise out of sleep [81]. It is unclear of whether this reflects a change in migraine circadian pattern or is related to increased likelihood of nighttime awakenings in older age. Most recently, a study examining differences in morning vs. afternoon headaches reported that phenotypically, morning onset headaches may reflect migraine phenotypically and afternoon onset headaches may reflect tension type headaches [15]. Lastly, limited data on morningness/eveningness preference (chronotype) reveal no clear preferences in those with migraine vs. without migraine [76]. Larger, prospective studies are needed to better characterize whether timing of headache onset supports a circadian rhythmicity in migraine.

Melatonin Studies and Migraine

Prior studies have reported on melatonin level changes in adults and children with migraine, with mixed results. Lower nocturnal urinary melatonin levels (or its metabolites) were reported in women with menstrually related migraine vs. controls (irrespective of menstrual cycle status), during the ictal migrainous phase compared to the interictal one, and in patients with chronic migraine compared to controls, but not in patients with episodic migraine compared to controls [82–85]. A more recent study in women with chronic migraine reported no differences in markers of circadian phase (dim-light melatonin onset [DLMO], sleep midpoint and phase angle) with controls, but found that higher attack frequency was associated with DLMO and later sleep midpoint [86]. Phase delay was previously reported in patients with chronic migraine compared to controls [87]. Of note, studies evaluating migraine comorbidities have reported that low melatonin levels were significantly influenced by comorbid insomnia and depression [87, 88]. Taken together, the research suggests no convincing differences in melatonin measures or delayed phase in those with episodic migraine but perhaps for those with the highest chronic migraine disease burden (highest headache frequency or comorbid insomnia and depression), although prior research has been limited by smaller numbers of patients and in some cases there were limitations in accounting for phase misalignment.

Melatonin has been tested as a migraine prophylactic treatment in pediatric and adult populations and as an acute treatment in children. One study of adults with episodic migraine reported that nightly use of melatonin 3 mg had similar efficacy as amitriptyline and better efficacy than placebo (2.7 less headache days per month vs. 2.2 less headache days per month vs. 1.1 days per month) [89]. Another study in adults reported that melatonin was not superior to placebo in reducing migraine monthly attack frequency [90], although this was a lower dose of extended release formulation than the more commonly used immediate release dosage modeled after jet-lag studies [91]. In children, melatonin demonstrated similar reduction in migraine attack frequency and better tolerability compared to amitriptyline in one study of patients with either episodic or chronic migraine [92]. Another placebo-controlled trial of melatonin in children as a preventive stopped early due to slow enrollment and high dropout rate, with interim analysis reporting that melatonin (3 or 6 mg) was not superior to placebo [93]. Melatonin has been trialed as an abortive medication for migraine in the pediatric population and is superior over placebo in pain reduction, displaying a dose-response effect and allowing for additional pain-relief through napping after treatment [94]. Both napping and a higher dosage of melatonin (mg/kg) were independently associated with pain reduction [94]. Compared with other migraine preventive medications, melatonin has minimal evidence to support its benefit as a migraine preventive in adults and children and one study supporting its use as a PRN (with high risk of napping) in children.

The Neurobiology of Sleep and Migraine

Neuroscientific evidence supports a shared pathophysiology between migraine and sleep disturbances, although there have been limited direct studies linking the two. Key players include shared subcortical structures (such as the hypothalamus), common mediating signaling molecules (neurotransmitters, neuropeptides, and hormones), and the CNS waste removal system, the glymphatic system.

The hypothalamus plays an important role in initiating sleep and wakefulness via a "flip-flop switch", dysfunction of which has been noted in insomnia [95]. In migraine, PET imaging evidence supports early hypothalamic involvement in a migraine attack [26••]. It is plausible that early hypothalamic involvement during the migraine prodrome mediates sleep changes prior to an attack.

Furthermore, neuropeptides under hypothalamic influence may be involved in sleep-migraine pathophysiology. Serotonin (5-HT) generally promotes wakefulness [95] and is released early in a migraine attack [96]. Serotonin release may contribute or be a marker of the perception of sleep disturbance as a migraine trigger. Orexin is important for sleep-wakefulness and is elevated in the CSF of those with chronic migraine [97]; however, a randomized controlled trial of an orexin antagonist in humans had negative results [98]. Lastly, pituitary adenylate cyclase activating peptide (PACAP) has been found to be elevated during migraine attacks [99] and is implicated in the activity of the retinohypothalamic tract in the suprachiastmatic nucleus of the hypothalamus, the "master clock" involved in circadian rhythm [100].

The glymphatic system is primarily active during sleep to remove interstitial waste [101] and cortical spreading depression in mice resulted in temporary impairment of glymphatic flow [102]. However, it is unknown whether chronic sleep disruption or CSD could result in accumulation of more toxic substances and contribute to disease pathology.

Conclusions

Sleep symptoms are commonly reported by patients with migraine and addressing them is an important part of management. Patients with migraine report poor sleep quality and high rates of insomnia symptoms interictally. Treatment of comorbid insomnia with CBT-I in patients with chronic migraine shows significant improvement on their headache burden. A subset of patients may be at risk for sleep apnea due to comorbidities, but early objective studies do not suggest that migraine is a risk factor for sleep apnea. Attack-related sleep changes are most common in the prodrome and may represent early activation of the hypothalamus rather than migraine triggers. There is minimal evidence that migraine is under circadian influence, but further studies are warranted. At the present time, the development of clinical guidelines to approach sleep symptoms and broader clinical trial interventions on insomnia in those with episodic migraine would be clinically valuable.

Author Contributions MD and AV wrote the main manuscript text and MD prepared Fig. 1. All authors reviewed and approved the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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•• Of major importance

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