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Sleep Disorders and Migraine: Review of Literature and Potential Pathophysiology Mechanisms

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Abstract

Migraine shares a complex and poorly understood relationship with sleep. Patients consistently report poor sleep prior to migraine attacks and during them, identifying poor sleep as a migraine trigger. However, anecdotally, sleep is reported to serve a therapeutic role in terminating headache. Are the associations between migraine and sleep simply the result of various bidirectional relationships? A growing body of evidence suggests there may be a common underlying etiology as well. Our objective was to review studies of sleep and migraine from the last 2 decades utilizing validated subjective and objective measures of sleep and to explore potential mechanisms underlying this complex relationship by incorporating recent advances in neuroscience. We specifically focus on insomnia, obstructive sleep apnea, parasomnias, sleep related movement disorders, and REM sleep related disorders and their relationship to migraine. Parts of brainstem-cortical networks involved in sleep physiology are unintentionally being identified as important factors in the common migraine pathway. Recent discoveries on anatomic localization (the hypothalamus as a key and early mediator in the pathophysiology of migraine), common mediating signaling molecules (such as serotonin and dopamine), and the discovery of a new CNS

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waste removal system, the glymphatic system, all point to a common pathophysiology manifesting in migraine and sleep problems.

Keywords

sleep; migraine; insomnia; apnea; glymphatic system

INTRODUCTION

Sleep disturbances and migraine share a complex and poorly understood relationship. Patients with migraine have consistently reported poor sleep both precipitating and during attacks. Sleep is frequently reported as having a therapeutic role in terminating the pain of an acute migraine attack; however, patients often feel fatigued in the postdrome phase.[1] Physicians regularly consider sleep when treating migraine – frequently selecting medications with sedative side effects in an attempt to treat sleep as a migraine trigger as well as enhance the perceived therapeutic role of sleep in terminating a migraine attack. Despite these common clinical observations and treatment goals, the relationship between sleep and migraine has only recently garnered attention.

Over the last 2 decades, several significant studies using validated subjective and objective measures of sleep (such as polysomnography) have confirmed and/ or modified long-held clinical observations. Recent neuroscience discoveries have also more clearly delineated the role of sleep in overall long-term brain health (for example, the proposed role of the recently discovered glymphatic system). This review aimed to: highlight findings from clinical research on sleep and migraine which point toward shared underlying mechanisms and to propose potential biological mechanisms to explain the strongest of the findings. As our intended audience is headache experts, we begin with a brief overview of sleep pathophysiology, followed by a discussion of key findings linking migraine and sleep disorders and conclude with a discussion of possible common biologic mechanisms.

NORMAL SLEEP PATHOPHYSIOLOGY

Why do humans sleep? The function to this great mystery is still unknown. However, there is a strong consensus that sleep, especially during the deeper stages of sleep, likely performs a restorative role of daytime activities.[2] On a biochemical level, it is thought that sleep functions to clear the brain of waste products that build up over the course of the day.[3] The recent discovery of the glymphatic system – a CNS clearing system that works primarily during sleep – provides the possibility for such a mechanism.[4]

SLEEP/WAKE MECHANISMS

The biological processes that initiate and maintain sleep and wakefulness have been more clearly defined. At the center of the current model is a “flip-flop switch” located in the hypothalamus that can abruptly and simultaneously promote sleep and inhibit wakefulness (and vice versa).[5] During wakefulness and REM sleep (also a time of increased cortical activity), the hypothalamus augments 2 major pathways, one which consists of acetylcholine

producing brainstem nuclei that activate the cerebral cortex via the thalamus, and the other that is composed of different brainstem nuclei, which more broadly project directly to the cortex. When one is ready for sleep, the hypothalamus can rather abruptly shut off the augmentation of wakefulness pathways and simultaneously turn on sleep promoting pathways, which originate from within the hypothalamus and send inhibitory output to arousal pathways in the brainstem and hypothalamus.[5,6]

Several important physiologic changes occur during sleep and are defined by different sleep stages. Once someone falls asleep, cortical activity (as measured by EEG) slows down quickly (over seconds to 1 minute)[7] into an NREM sleep pattern (see Table 1). The waves become progressively slower until they consistently reach a delta wave frequency, at which point the sleep stage is defined as slow wave sleep or restorative sleep, with a typical cycle lasting 40 minutes to over an hour.[6] This slow wave sleep has long been felt to play a restorative role of daytime activities.[2] After a slow wave sleep cycle, there is an abrupt transition (over a few seconds) into REM sleep, which is attributed to both the hypothalamic flip-flop switch as well as another that exists in the mesopontine tegmentum in the brainstem.[8] REM sleep is manifested as increased cortical activity in the EEG, a complete loss of muscle tone aside from rapid eye movements on the EMG, and dreaming/nightmares. This entire sleep cycle reoccurs many times throughout the course of the night, with rapid transitions between NREM and REM sleep and occasional periods of wakefulness.[6] Typically, as we age, the percentage of time spent in slow-wave or restorative sleep decreases and the number of nighttime arousals increases.[9]

SLEEP DISORDERS AND THEIR RELATIONSHIP TO MIGRAINE

Insomnia.—

Insomnia is defined as difficulty with sleep initiation or maintenance with daytime consequences, despite adequate opportunity and circumstances to sleep.[10] It is the most prevalent sleep complaint, with approximately one-third of the population reporting an insomnia symptom[11] and 6% of the general population meeting a chronic insomnia diagnosis (insomnia that occurs at least 3 times per week for 3 months or longer).[12] Insomnia has been termed a disorder of physiologic hyperarousal – with increased heart rate variability, elevations in evening cortisol levels (a time where cortisol is typically at its diurnal nadir), and high frequency activity in the EEG.[13] One proposed mechanism, supported by animal studies, is a malfunction in the hypothalamic flip-flop switch responsible for transitioning between sleep and wakefulness.[5,14]

Patients with migraine report increased insomnia complaints interictally – including difficulty initiating sleep, staying asleep, poor sleep quality, self-reported decreased total sleep time, excessive daytime sleepiness, and lack of refreshment after sleep.[15–25] Such findings persist when controlling for comorbid anxiety and depression.[23] These frequent subjective complaints of insomnia among persons with migraine have also led to the notion that poor sleep may be a part of the migraine endophenotype. To this end, several studies have examined the baseline polysomnography data of patients with migraine.[18,20,26–30] Although sleep latency does not appear to be related to migraine interictally,[20,31] important measures of sleep quality including sleep efficiency and amount of slow wave sleep are

decreased in patients with migraine.[27–29,31] REM sleep, which has long been implicated to play a role in various headache disorders (such as cluster and hypnic headache), may also be affected in patients with migraine at baseline, with smaller studies reporting patients with migraine have a lower arousal index during REM sleep as well as lower cyclic alternating pattern at baseline.[27,32,33] Together, these findings suggest possible brainstem dysfunction in the networks important in switching between sleep stages.

Sleep may be directly interrupted by a headache attack as well as altered prior to a migraine attack. Two-thirds of patients with migraine report at least occasional headaches awakening them from sleep, often arising out of REM and slow wave sleep.[17,24,34,35] Sleep is disturbed by increased awakenings and decreased amounts of slow wave (restorative) 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.[18,31] To this effect, patients also report insomnia in the night before an early morning migraine attack.[34] Interestingly, early morning migraine attacks increase with age such that they occur in only 16% of those in their twenties and in 58% of those >60 years old.[36] Given that older adults are known to have less slow wave sleep and more frequent nighttime arousals,[9] this may simply reflect that older adults are more likely to wake up with a headache in the middle of the night – or more interestingly, this may reflect a common etiology of deterioration in brainstem and hypothalamic sleep promoting mechanisms.

With respect to clinical implications, insomnia is under-recognized and undertreated in patients with migraine.[19] Treatment of insomnia in migraine patients with CBT for insomnia shows significant benefit in sleep efficiency (as measured by actigraphy) as well as reductions in headache frequency.[37] Sleep disturbances may be the manifestation of a common shared biology in at least a subset of patients with migraine, so should be screened and addressed.

Obstructive Sleep Apnea (OSA).—

The diagnosis of obstructive sleep apnea requires signs/symptoms of sleep apnea (associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea) or an associated medical or psychiatric disorder (hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder) coupled with 5 or more predominantly obstructive respiratory events per hour of sleep during PSG.[10] In the absence of associated symptoms or disorders, ≥15 obstructive respiratory events per hour satisfies the criteria.[10]

Frequent morning headaches or awakening headaches, common symptoms in those with OSA, are directly linked to hypoxemia and hypercapnia[38,39]and typically resolve with its treatment.[38,40–43] Patients with chronic daily headache are more likely to be daily snorers than control subjects and it has been suggested that they be screened for sleep apnea.[44] In both clinical studies of children and adults, it has been reported that migraine that occurs in the morning is associated with breathing difficulties,[16,45] snoring,[16,24] and sleep apnea.[16,29]

Population based polysomnographic studies report patients with migraine have similar rates of sleep apnea as the general population.[30,46] In particular, the Kristiansen et al

comprehensive population based study in Norway, which employed a stepwise screening of a national health registry, followed by clinical interview and polysomnography, reported not only similar rates of sleep apnea among patients with migraine without aura, migraine with aura, and the general population, but also failed to observe a difference between the severity of OSA among these groups.[30]

In summary, while headaches are common symptoms of sleep disordered breathing and snoring is a risk factor for chronic daily headache and chronic migraine,[44] population based studies do not find increased rates of OSA in those with migraine. Although the rates of OSA are not clearly higher among those with migraine, patients with migraine and OSA do share some common risk factors, such as obesity. Furthermore, it is possible that those with migraine have a lower threshold for the hypoxemia inducing headaches of OSA, which contribute to their overall headache burden. Lastly, the different findings between clinical and population studies may reflect the methodology utilized, given that both migraine and OSA are commonly encountered in the clinical setting, but are under-recognized in the general population. Given that OSA is underdiagnosed in the general population and a potential modifiable risk factor for future vascular events, clinical evaluation of migraine patients should include screening of OSA when appropriate.

Parasomnias And Sleep-Related Movement Disorders.—

Parasomnias and sleep-related movement disorders are implicated in several neurologic diseases, particularly those with dopaminergic dysfunction, which is known to play a role in the migraine prodrome.[47,48] Several studies have reported that the non-REM parasomnia of somnambulism (sleep walking) and the sleep-related movement disorders of bruxism and restless legs syndrome are common in those with migraine, further implicating dopamine as an important neurotransmitter in migraine pathophysiology.

Somnambulism.—

Studies of both children and retrospective recall by adults with migraine suggest higher rates of somnambulism during childhood, more strongly in patients with aura. Parental report indicates that children with migraine with aura have higher rates of somnambulism (13%) than children with migraine without aura or control subjects (both approximately 3%).[15] Somnambulism was found to be increased in children with either migraine or tension type headache in a population based study investigating childhood periodic syndromes.[49] Other disorders such as motion sickness, recurrent limb pain, recurrent abdominal pain, sleep talking, and bruxism were also increased in children with headache.[49] Among adult patients with headache, a significantly higher percentage of patients with migraine reported childhood history of somnambulism compared to other headache types (33% vs 5%).[50] Migraine and any headache type is also associated to PSG-confirmed somnambulism in adults – a relationship that persists when controlling for depression, daytime sleepiness, and insomnia severity index.[51]

Bruxism.—

The correlation of bruxism with temporomandibular joint dysfunction (TMD), known to be co-morbid with migraine, makes it a particularly frequent complaint among patients with

migraine.[52] Although many studies of sleep bruxism have not used ICHD criteria, instead referring to general reports of headache,[53] one clinical sample of patients seeking treatment in a TMD and orofacial pain clinic utilizing ICHD criteria found that sleep bruxism was associated with a diagnosis of chronic migraine, with a trend toward episodic migraine, but not with tension type headache.[54] Although a well-recognized association, the etiology of the bruxism-migraine relationship is less well understood. It is possible that bruxism and TMD trigger migraine attacks through increased peripheral activation of the trigeminal nerve, or that patients with migraine are more susceptible to pain from TMD secondary to central sensitization. Lastly, the same central etiologies proposed for sleep bruxism may possibly directly contribute to migraine (including sleep microarousals and mechanisms involved in sleep stage transitions).[55]

Restless legs syndrome (RLS).—

There have been over 24 studies examining whether there is an association between migraine and restless legs syndrome, with the overwhelming majority finding an increased risk of RLS in those with migraine, with the effect size considerably higher in case-control studies (OR 4.2 [3.1–5.7]) than in cohort studies (OR 1.2 [1.1–1.3]).[56] Migraine with aura does not appear to confer an increased risk of RLS compared with migraine.[57–60] Migraine is also associated with more severe symptoms of RLS.[61] These replicated findings of RLS with migraine may be reflected in the PSG observations of decreases in sleep efficiency or in the subjective complaints of difficulty initiating sleep. Pathophysiologically, this association brings attention to the role of dopamine in both migraine and RLS. As noted above, dopamine is implicated in the prodromal symptoms of migraine – many of which are thought to possibly be hypothalamic in origin.[47] RLS is thought to be the result of a dysfunction of the dopaminergic system of the A11 neurons descending from the hypothalamus to the spinal cord.[62]

REM-sleep related behaviors and nightmares.— REM-sleep behavior disorder (RBD) is a rare disorder in which there is documented REM sleep without atonia as well as either polysomnographically captured episodes of behavior/vocalizations arising from REM sleep or the presumption of these arising from REM based on reports of dream enactment.[10] To our knowledge, there have been no polysomnographic studies examining RBD in patients with headache. One study utilizing a validated RBD questionnaire reported that migraine patients had a higher frequency of dream-enacting behavior (DEB) compared to controls (24.2% v 14.3%), which was independent of headache frequency or intensity.[63] Of note, the rates of RBD were much higher in the control population than what is known from the general population (approximately 1%), likely due to low specificity of the questionnaire. Migraine patients with DEB had worse headache-related disability compared to migraine patients without DEB.[63] Future PSG studies of patients with RBD and migraine may provide an interesting window into how the extremes of altered REM sleep may be manifested in those with migraine.

Patients with migraine also report increased frequency of nightmares. [64,65] Although the significance of this is unknown, it may reflect more frequent awakenings, such as during

REM sleep. Further research should explore whether self-report of nightmares reflects alterations in sleep architecture among patients with migraine.

NARCOLEPSY

There is limited evidence to suggest a relationship between migraine and narcolepsy. One study reported that although there was not an increased rate of migraine among narcolepsy patients, there was an increased rate of tension type headache.[66] Another uncontrolled study reported an increased rate of migraine in narcolepsy patients compared to the general population[67] and a more recent controlled study also reported increased rate of migraine in narcolepsy patients (23.5%) and those with primary hypersomnia (41.2%) (although the prevalence of migraine in controls was quite low at 4.9%).[68] Further research is needed in this area to elucidate the existence of such a relationship.

PATHOPHYSIOLOGY AND POTENTIAL MECHANISMS

The complex relationship between sleep and migraine has typically been interpreted as a series of bidirectional interactions (for example, having a nocturnal migraine may disrupt one's sleep, or that sleep is frequently used to abort a migraine attack). Our review of the most recent literature on sleep and migraine suggests that although there are some bidirectional relationships among these varied interactions, a more comprehensive approach may be to view migraine and sleep problems as manifestations of a common underlying pathophysiology. There is increasing neuroscientific evidence to support such a proposition, with new discoveries on anatomic localization (the importance of common subcortical structures in both sleep and migraine, such as the hypothalamus), roles of common mediating signaling molecules (neurotransmitters, neuropeptides, and hormones), and the discovery of a new CNS waste removal system, the glymphatic system. We propose some mechanisms to explain the associations reported above.

DOES POOR SLEEP TRIGGER MIGRAINE ATTACK(S)?

Whether insomnia is part of the migraine prodrome or actually incites a migraine attack is a complicated and interesting question. In our review of the literature, we noted that frequent nighttime awakenings, but not objectively decreased total sleep time, precede sleep-related migraine attacks. Although it has long been suggested that poor sleep may lower pain thresholds in all humans, a recent study in normal volunteers found a significant loss of pain inhibition and an increase in spontaneous pain only in those with frequent awakenings (and not in those with partial sleep deprivation), suggesting that sleep continuity disturbance but not simple sleep restriction lowered pain thresholds.[69] What is the mechanism which might explain this observation? Serotonin (5-HT), which has diverse roles in many human behaviors including sleep, mood (depression and anxiety), appetite, sexual function, and pain, may be playing a joint function in this process. With respect to sleep, serotonin appears to promote wakefulness and inhibit REM sleep. With respect to migraine, the evidence suggests that individuals with migraine exist in a low serotonin state interictally, with mobilization of 5HT from intracellular stores early in a migraine attack.[70,71] Given that patients with sleep-related migraine are found to have increased nighttime awakenings in the

night preceding headache, it is possible that serotonin release may contribute or be a marker of this observation. Although it is not clear how ictally elevated serotonin levels may ultimately participate in the trigeminovascular nociceptive pathway, animal models exposed to high serotonergic states have increased CSD waves.[72] Given that all brain serotonin is believed to be produced in the brainstem (from the dorsal raphe nucleus in the pons and midbrain), there has been research interest in implicating this structure in the pathogenesis of migraine. Since the dorsal raphe nucleus is pivotal in transition from NREM to REM sleep – in particular, the cessation of firing of the serotonergic neurons is necessary to initiate REM.[73] As noted by Nayak, there is decreased cycling within REM sleep (the "micro-architecture" of sleep) in those with migraine – possibly reflecting a dysfunction of the subcortical serotoninergic system.[27]

Furthermore, the subsequent targets of signals from the dorsal raphe nucleus are diverse, involving both cortical and subcortical regions (including the amygdala, hypothalamus, locus coeruleus, and pontine reticular formation). One of these targets, the hypothalamus, has been proposed as a central and early player in the pathophysiology of a migraine attack, as PET imaging revealed that hypothalamic activity is altered during the 24 hours prior to pain onset, with altered functional coupling with the spinal trigeminal nuclei and the dorsal rostral pons occurring soon thereafter (pre-ictally and in the early pain phase).[74] The hypothalamus is the central regulator of sleep and wakefulness, with the preoptic hypothalamus synthesizing GABA (which subsequently inhibits monoaminergic systems such as the serotonergic system noted above). [5,75] The hypothalamus is also favored to be implicated in migraine secondary to its role in the production of gonadotropin-releasing hormone (stimulating FSH and LH, and ultimately estrogen release from the ovaries).

In addition to serotonin, dopamine has been implicated as having involvement during the premonitory phase of migraine during which yawning, drowsiness, mood changes, irritability, and hyperactivity are reported,[47] with experimental data from rats showing that dopamine can modulate neuronal firing in the trigeminocervical complex.[62] The dopaminergic system is also important in sleep-arousal pathways, primarily promoting arousal via hypothalamic input into the periaqueductal gray dopaminergic neurons.[5] As noted previously, patients with migraine are at increased risk for RLS, where there is a dysfunction of the dopaminergic system of the A11 neurons descending from the hypothalamus to the spinal cord.[63] Interestingly, patients with migraine and comorbid RLS have higher frequency of premonitory symptoms than those without RLS,[48] and this may reflect a shared dysfunction in the dopaminergic system in a subset of patients.

HOW CAN SLEEP TERMINATE A MIGRAINE? WHY DOES IT NOT KEEP BEING RESTORATIVE IN CHRONIC MIGRAINE?

One common yet unexplained observation is that sleep can often terminate a migraine attack. In another common clinical observation, this restorative impact of sleep seems to not be as effective in those with chronic migraine. This raises the still unanswered question as to why humans require sleep, and the commonly held notion that sleep, particularly in the deepest stages, allows for the consolidation and restoration of the brain's daytime activity. A

newly discovered CNS waste clearing system, the glymphatic system, has provided one possible explanation. The glymphatic system is primarily active during sleep with its primary purpose of interstitial waste removal (such as beta-amyloid) via a perivascular system.[4] The perivascular space is created by an external barrier of astrocytic end feet that express the Aquaporin 4 water channel and an internal barrier of endothelial cells. In mice, this system is much more active during sleep.[77] Though the role of glymphatic system during sleep in migraine has not been studied, the proposed restorative role that the glymphatic system plays in CNS during sleep may explain the often therapeutic role of sleep in migraine attacks. Furthermore, any migraine induced disruption in the functioning of the glymphatic system may contribute to pathophysiology of migraine as a global CNS disorder. Recently, Schain et al were able to demonstrate that cortical spreading depression resulted in temporary impairment of glymphatic flow in a mouse model via closure of the perivascular space for several minutes after CSD followed by gradual recovery over 30 minutes.[78] To our knowledge, this is the first experiment directly implicating the glymphatic system in the pathophysiology of migraine. Given that glymphatic system is primarily active during sleep, one could propose that sleep disruption could in fact lead to an accumulation of waste products, which may contribute to the pathophysiology of a migraine. Additionally, if the chronification of migraine itself were to result in chronic sleep disruption, this would result in the accumulation of more toxic substances, such as beta-amyloid and metalloproteinases. Perhaps this may offer one explanation as to why sleep, at least anecdotally, loses its potent attack terminating role in those with chronic migraine.

CONCLUSION

The complex relationships between sleep and migraine point to a common shared pathophysiology. Although this topic has received significantly more attention over the last 2 decades, there are still many knowledge gaps. Throughout our review, we have identified several areas in need of further research. Furthermore, our clinical and research approaches should be tailored to view sleep problems as intimately linked to migraine pathophysiology, in at least a subset of patients. Treatment of sleep problems in patients with migraine may result in overall decrease in headache days and disability.

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Table 1.

—Select Sleep Parameter Definitions

Sleep latency	The amount of time it takes to initiate sleep once one is in bed and ready to sleep
NREM sleep	Includes stages 1 and 2 as well as slow wave sleep. The EEG is characterized by higher voltage and slower waves
Slow wave sleep	Previously termed stage 3 and 4 sleep. This EEG is characterized by delta waves. It is sometimes thought of as “deep sleep” or “restorative sleep”
REM sleep	A period of increased cortical activity and absent muscle tone aside from rapid eye movements. It is also a period where dreaming may take place. The EEG is defined by lower voltage, higher frequency theta activity
Sleep efficiency	The amount of time asleep divided by the total amount of time in bed