Sleep and headaches
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Introduction

Overview

There is an intimate association between headaches and sleep. Some headaches are triggered by sleep, other forms occur exclusively during sleep, and yet some are ameliorated by sleep. The author reviews the different forms of sleep-related headaches and describes the manifestations of those that are cause for concern. A section on management closes the article.

Key points

• There is an intimate relationship between sleep and headaches.
• Certain types of headaches may be associated with specific stages of sleep and, thereby, lead to sleep disruption.
• Migraine headaches, cluster headaches, paroxysmal hemicrania, hypnic headache, and headache on awakening are the most emblematic sleep-related headache disorders.
• Migraine headaches may be provoked by sleep, but the most common association is sleep following a migraine attack.
• Proper sleep hygiene is paramount to aid in the prevention of sleep-related headaches.

Historical note and terminology

Practitioners of medicine are aware of the intimate relationship between sleep and headaches. In 1873 Liveing wrote about the effect of sleep in terminating an attack of headache (Lance et al 1983; Sahota and Dexter 1990). In 1913 Freud mentioned “headache-dreams” and gave a psychodynamic interpretation of their occurrence (Freud 1988). Early morning headaches were cited by Bing in 1945 (Sahota and Dexter 1990), and later, Gans wrote about treating migraines with sleep-rationing (Gans 1951). Dexter and Weitzman reported the relationship between headaches and sleep stage patterns (Dexter and Weitzman 1970), and Lance and colleagues provided a neurophysiological account of the relationship between the nucleus locus ceruleus and mechanisms underlying migraine (Lance et al 1983). The intriguing association between paroxysmal hemicrania and REM sleep (Kayed et al 1978) attracted attention to the circadian sleep rhythms and their influence on triggering headaches. The neurotransmitter serotonin has been extensively investigated by researchers of sleep and of headache syndromes, and is often cited as a common link between the two. Sleep may trigger or terminate headaches, and different varieties of headaches may occur with any of the stages of sleep or sleep loss. Well-defined associations between sleep disorders and headache disorders include sleep-phase related headaches (Cohen and Kaube 2004), sleep apnea and headache, and parasomnias and headaches.

The International Classification of Sleep Disorders-3 (ICSD-3) recognizes the following headache disorders in association with sleep: migraine, cluster headache, chronic paroxysmal hemicrania, hypnic headache, and other medical, neurologic, psychiatric, and sleep disorders–associated conditions (American Academy of Sleep Medicine 2014). The diagnostic criteria require that the patient complain of headache during sleep or on awakening from sleep.

Clinical manifestations

Presentation and course

Certain types of headaches may be associated with specific stages of sleep and thereby lead to sleep disruption. Migraine attacks have been described in association with sleep stages 3, 4, and REM. Cluster headaches and chronic paroxysmal hemicrania have been linked with stage REM. Sleep-related migraine attacks similar to daytime episodes are characterized by unilateral throbbing headache associated with nausea and vomiting, scotomata, visual field defects, photophobia, paresthesias, and sometimes hemiparesis or aphasia. Migraines are highly idiosyncratic and not all symptoms are present. Attacks last several hours to a few days.
Cluster headaches that commonly occur during sleep are characterized by severe unilateral, periorbital, malar, and temporal pain with lacrimation, nasal engorgement, rhinorrhea, forehead sweating, and flushing of the malar area. Attacks last no more than 2 hours and may occur several times daily, sometimes at the same time of the day or night, commencing and terminating abruptly. Spontaneous remissions lasting several months characterize the syndrome. Transient recurrent situational insomnia in association with cluster headache resolves after the headache syndrome subsides (Sahota and Dexter 1993). Chronic insomnia and shift work seem to be common among Arctic cluster headache patients. In a small study of Arctic workers, insomnia was significantly associated with shift work and longer-lasting cluster bouts (Ofte et al 2013). Eighty percent often had headache attacks during sleep, in particular, between 24:00 am and 04:00 am. Shift workers were significantly more likely to see lack of sleep as a cluster attack trigger than daytime workers, supporting the idea of cluster headache as a circadian rhythm disorder.

In chronic paroxysmal hemicrania, attacks of severe pain are shorter than with cluster headache, but they are more frequent and are also associated with conjunctival hyperemia, rhinorrhea, and more rarely Horner syndrome. They may occur predominantly at night, usually at the same hour, and do not remit spontaneously. The sometimes close linkage to REM sleep has led to the descriptive term "REM sleep-locked headache."

Headaches may occur on awakening with a variety of disorders. Although common in children with brain tumors, they appear in only 5% of adults with brain tumors. In the sleep apnea syndrome, patients often complain of diffuse headache in the morning localized to the frontal region, but the incidence is not related to the severity of the disease (Aldrich and Chauncey 1990). The intensity of pain is mild to moderate and tends to disappear shortly after getting out of bed. Morning headache may not be more common in patients with sleep apnea syndrome than in other sleep disorders, but the successful treatment of sleep apnea is associated with significant improvement of chronic headache in 30% of patients (Poceta and Dalesio 1995). In patients with sleep apnea syndrome, prolonged afternoon naps may also be followed by headache. Headaches on awakening in the morning may also occur in relation to bruxism, systemic hypertension, depression, muscle-contraction headache, alcohol intoxication, and sinus inflammation. In a study of 721 consecutive patients comparing the characteristics of idiopathic intracranial hypertension in men and women (Bruce et al 2009), the authors found that men were more likely to have sleep apnea (24% vs. 4%, p < 0.001) and were older (37 vs. 28 years, p = 0.02). Men were less likely to report headache (55% vs. 75%, p < 0.001) as their first symptom of intracranial hypertension, but had more visual disturbances (35% vs. 20%, p = 0.005).

Chronic headaches in children may be seen in association with decreased duration of sleep at night, poor sleep hygiene, fragmentation of sleep, increased number of somnambulism, somniloquy, and enuresis events, and nocturnal snoring (Smyers 1999). A study found that children with headaches have more excessive daytime sleepiness, narcolepsy, and insomnia than children without headaches (p<0.005), whereas sleep apnea and parasomnias may be more specific for genuine migraines and not for headaches in general (Luc et al 2006). Pediatricians should inquire about daytime sleepiness, narcolepsy, and insomnia in children with headaches. In a polysomnographic study of children with headaches, the authors found results supporting an association between migraine and sleep-disordered breathing, and between tension headache and bruxism (Vendrame et al 2008). Reduced REM and slow-wave sleep in severe and chronic migraine headache patients suggests an intrinsic relationship between sleep and headache disorders.

Hypnic headache is a benign headache disorder of the late middle-aged and the elderly, characterized by regular awakenings from sleep at a constant time of night (Raskin 1988). The headache is diffuse and bilateral, lasts 30 to 60 minutes, and is sometimes associated with a dream. Dodick and colleagues reported 19 cases with a mean age of headache onset of 60.5 + 9 years (Dodick et al 1998). Patients were generally awakened between 1 AM and 3 AM; 3 patients reported that a similar headache could occur during daytime naps as well. In 68% of patients headache frequency was 4 nights per week, with resolution occurring within 2 hours. As more patients are described, the number of unilateral hypnic headaches reported has increased (Gould and Silberstein 1997). In a review of 71 cases, Evers and Goadsby described the following characteristics: age at onset, 63 years, female 63%; duration of attack, 67+ 44 minutes; frequency of attacks, 1.2 per 24 hours; moderate intensity of pain 67%, bilateral pain 61%, diffuse pain 56% (Evers and Goadsby 2003). Hypnic headache is very rare in childhood; its clinical features are inconsistent, but in 1 review study, autonomic symptoms were absent in all patients. Successful treatment with melatonin was reported in 2 out of 5 patients (Silva-Nêto and Almeida 2015). In 1 retrospective study of 40 patients (80% females) with hypnic headache and mean follow-up of 929 days, the average age of headache onset was 62 years (range 44 to 86) (Tariq et al 2016). Twenty (50%) patients had previous history of migraine, 5% had bilateral cranial autonomic features, and 40% underlying sleep abnormalities. The average duration per day and frequency per month of headaches were 186
minutes (range 30 to 720 minutes) and 21 days (range 5 to 30), respectively. The best response was obtained with lithium (7 out of 10 complete response and 2 out of 10 moderate response). Caffeine induced a complete response in 6 out of 21 and a moderate response in 9 out of 21 subjects.

The exploding head syndrome or “snapping of the brain” is characterized by flashing lights and sounds during the night that terrify patients (Green 2001). Pain is not present. Polysomnographic studies have shown that the attacks take place during all stages of sleep including REM sleep, without evidence of epileptogenic discharges (Raskin 1988). There is 1 case report of exploding head syndrome followed by sleep paralysis and migraine (Evans 2006).

Hemicrania horologica or clock-like hemicrania is a rare disorder with headaches that occur with clock-like precision every 60 minutes, day and night, lasting 15 minutes (Granella and D'Andrea 2003). Hemicrania horologica differs from chronic paroxysmal hemicrania in the lack of autonomic signs, the clock-like regularity over 24 hours, and the response to nonsteroidal anti-inflammatory drugs in addition to indomethacin. Unlike hypnic headache, attacks also occur during the day.

Clenching and grinding of teeth during sleep, or bruxism, is a sleep-related movement disorder occurring predominantly in stages 1 and 2 of sleep, although it has also been noted in REM sleep. Hundreds of events occurring during the night may lead to abnormal wear of the teeth, temporomandibular joint disorder, and jaw pain. Some patients with bruxism have associated muscle-contraction headaches. In one study of carefully classified patients, the authors identified a clear relation between muscle-contraction headaches and temporomandibular symptoms, depression, anxiety, poor sleep, and impairments of oral function (Caspersen et al 2013). The authors concluded that the findings indicate a close, but incomplete, overlap between muscle-contraction headaches and temporomandibular joint disorder, advocating for further research.

Chronic insomnia and headaches along with memory deficit, depression, anxiety, irritability, and judgment and personality disorder form part of the postconcussion syndrome that develops following head trauma in susceptible patients. Polysomnographic studies immediately following severe head trauma have shown alpha-wave intrusion, increased amount of sleep spindles, decreased REM density, and enhanced muscle tone in REM sleep, while individual sleep stages become less distinct. Weeks to months following recovery of consciousness, stages 3, 4, and REM are decreased along with total sleep time. Sleep spindles are decreased and the polysomnogram is punctuated with numerous arousals and awakenings. The postconcussion syndrome appears within hours to days following head trauma and may persist for many months thereafter.

Self-reported snoring was associated with headache (odds ratio 1.5 with a 95% confidence interval) independent of other potential confounders in a study of 3323 middle-aged and elderly men in Denmark (Jennum et al 1994). Although obstructive sleep apnea could underlie such an association, lack of nocturnal measurements precluded the evaluation of that hypothesis.

Insomnia and daytime fatigue are common complaints in patients with chronic headache. A study of the prevalence and intensity of fatigue in chronic headache sufferers has shown that this group of patients feels more tired (especially the women) and does not sleep as well at night, especially the men (Spierings 1997). Fibromyalgia occurs in 35.6% of patients with chronic migraine, also known as transformed migraine, and this group of patients has a higher incidence of insomnia (Peres et al 2001b). In a study of 784 subjects, the prevalence of headache and headache frequency were higher in subjects referred for polysomnography for any sleep disturbance independently of obstructive sleep apnea, compared to general population controls (Beiske et al 2013).

Drugs used for treatment of sleep disorders may have headache as a common adverse event. Safety and tolerability data of modafinil from 6 double-blind, placebo-controlled studies evaluated 1529 outpatients randomized to modafinil 200 mg, 300 mg, 400 mg, or placebo once daily for up to 12 weeks. Headache appeared in 34% of patients receiving modafinil versus 23% receiving placebo (Roth et al 2007). Headache is also a common adverse effect in patients taking ramelteon for treatment of insomnia (Ermann et al 2006) and zolpidem extended-release 12.5 mg (Krystal et al 2008). Headache is the most common side effect reported by patients taking melatonin also for insomnia (Buysse et al 2005). Long-term treatment with amphetamines of patients with narcolepsy may provoke headache along with irritability, bad temper, and profuse sweating (Nishino and Mignot 2005).

Chiari type I malformation is characterized by herniation of the cerebellar tonsils through the foramen magnum (Ferré Masó et al 2014). This is associated with brain stem, medullary, and cranial nerve compression phenomena. The most
frequent symptoms are occipital headaches and dizziness. In addition, patients may have less well-known symptoms, including sleep-related respiratory abnormalities. Some studies report a 50% prevalence of sleep apnea-hypopnea syndrome (SAHS), probably associated with sudden death, in some cases of Chiari type I malformation. The identification of sleep apnea may lead to better treatment and improved quality of life.

**Prognosis and complications**

Sleep-related migraine, cluster headache, and chronic paroxysmal hemicrania are benign conditions that do not alter the lifespan of the individual. Work incapacity may occur during severe attacks, and global incapacity may occur if attacks are severe and frequent. In women, attacks may cease after menopause. Bruxism may lead to excessive and abnormal wear of the teeth, temporomandibular joint degeneration, and chronic headaches.

**Clinical vignette**

A 55-year-old man was evaluated in the clinic because of headaches that were occurring at night and on awakening. Several nights of the week he would wake up between midnight and 2 AM with a bifrontal headache that would disappear on getting out of bed. Most mornings he had a diffuse headache that tended to dissipate after breakfast. He also complained of loud snoring and excessive daytime sleepiness that he attributed to the awakenings caused by headaches. The patient was a physician. His colleagues had noted recent episodes of confusion that they felt were the consequence of sleepiness. On examination, he had an acromegalic facies. Deep tendon reflexes were increased and plantar responses were equivocally extensor on both sides. A polysomnographic study followed by a multiple sleep latency test showed a respiratory disturbance index of 28 events per hour and mild episodes of desaturation predominantly during REM sleep. Nocturnal REM sleep latency was 25 minutes. The multiple sleep latency test showed presence of REM sleep in the first nap and an average sleep latency of 3 minutes in 4 nap segments. A diagnosis of sleep apnea disorder and possible narcolepsy was made.

A CT scan of the head ordered by the neurologist and sleep specialist to further evaluate the abnormalities observed in the neurologic examination showed a mass compressing the floor of the third ventricle that the radiologist interpreted as a craniopharyngioma. The patient was referred for neurosurgical management that confirmed the radiological diagnosis.

Causes for concern in this patient are nocturnal headaches that improved on getting out of bed, episodes of confusion, and associated signs of neurologic involvement manifested by increased deep tendon reflexes and equivocal responses to plantar stimulation. Tumors of the floor of the third ventricle may cause excessive daytime sleepiness with REM sleep abnormalities in the polysomnographic study suggestive of narcolepsy. Mild acromegaly as a result of hypothalamic-pituitary dysfunction caused enlargement of the tongue and soft palate with sleep apnea disorder of moderate intensity that was a contributing factor to daytime sleepiness.

**Biological basis**

**Etiology and pathogenesis**

The pathophysiology and pharmacology of headache and sleep disorders involves a group of neural networks that likely underlie a shared clinical association. The obvious brainstem, hypothalamic, and thalamic convergence suggests a bidirectional influence, but it is difficult to differentiate between cause and effect, whereas a spurious relationship cannot be ruled out (Holland 2014). The cause of migraine, cluster headaches, and chronic paroxysmal hemicrania remains unknown, and the interaction between headaches and sleep is poorly understood. In rare instances, intracranial tumors cause severe headaches that awaken the patient at night. Meningitis causes insomnia because of head pain.

Migraine headaches may be provoked by sleep, but the most common association is sleep following a migraine attack. The “therapeutic” need for sleep in some patients having an attack of migraine may be related to the disorders of serotonin metabolism in migraine, but proof is lacking. Neural stimuli originating in the hypothalamus or brainstem may provoke changes in cerebral and extracranial circulation. The trigeminovascular system that promotes vasodilatation and release of calcitonin gene-related peptide and substance P (Moskowitz et al 1989) has been implicated in the mechanism of migraines because calcitonin gene-related peptide is elevated in the jugular venous blood of migraineurs during the attack (Goadsby et al 1990). Serotonin (5-HT) is released from platelets during migraine headaches, and 5-hydroxyindoleacetic acid, the main metabolite of serotonin, is excreted in excess in the
urine following a migraine attack. Sumatriptan (an agonist of the 5-HT1 receptor found in cerebral arteries, where it has an inhibitory effect) aborts the migraine headache. Methysergide (antagonist of the 5-HT2 receptor found mainly in temporal arteries, where it has an excitatory effect) also terminates migraines. Serotonin, implicated in mechanisms of NREM sleep, is a possible neurotransmitter link between migraine and sleep. In a study of 1283 migraineurs drawn from 1480 consecutive headache sufferers presenting for evaluation to a tertiary headache clinic, Kelman and Rains found that migraineurs were 84% female, with a mean age of 37.4 years (Kelman and Rains 2005). Groups were formed based on patient's average nocturnal sleep patterns, including short, normal, and long sleep groups, and were compared on headache variables. Sleep complaints were common and associated with headache in a sizable proportion of patients. Over half of migraineurs reported difficulty initiating and maintaining sleep at least occasionally. The short sleep group, who routinely slept 6 hours per night, exhibited the more severe headache patterns and more sleep-related headache. Sleep complaints occurred with greater frequency among chronic than episodic migraineurs. The authors indicated that prospective studies are needed to determine if normalizing sleep times in the short sleepers would impact headache threshold.

In 1 study, migraineurs showed a lower cyclic alternating pattern rate in NREM sleep and, in particular, a lower number of A1 phases (low-frequency, high-amplitude EEG bursts) compared with the controls (Della Marca et al 2006b). Migraineurs also showed a lower index of high-frequency EEG arousals during REM sleep. The reduction in cyclic alternating pattern rate was interpreted by the authors as a lower level of arousal fluctuation in NREM sleep. They suggested that the reduced arousal index in REM was due to a dysfunction in neural structures involved in both the control of REM sleep and the pathophysiology of migraine, including the hypothalamus and the brainstem.

The trigeminal autonomic cephalalgias are a group of primary headache disorders that includes cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and cranial autonomic features (SUNCT/SUNA) (Goadsby et al 2010). Hemicrania continua is often included with this group. Cluster headache shows a remarkable periodicity in its occurrence, suggesting a linkage to the circadian rhythm. The neurovascular hypothesis suggests excitation of autonomic fibers of the greater superficial petrosal nerve that would be responsible not only for lacrimation and conjunctival injection, but also for edema of the wall of the internal carotid artery with pain and ipsilateral Horner syndrome. The association between migraine attacks, cluster headache, chronic paroxysmal hemicrania, and REM sleep remains unexplained. Autonomic dysfunction was suggested in a 9-week actigraphic recording with repeated polysomnography of a patient with cluster headache, evaluating both sleep macrostructure and microstructure (Della Marca et al 2006a). During the acute bout the authors observed an irregular sleep-wake pattern and abnormalities of REM sleep. After the cluster phase these alterations remitted. The authors concluded that cluster headache was associated, at least in this patient, with sleep dysregulation involving the biological clock and the arousal mechanisms, particularly in REM sleep. They hypothesized that the abnormalities were consistent with posterior hypothalamic dysfunction.

Patients with cluster headache have a higher prevalence of sleep apnea, and a possible relationship between these 2 conditions has been proposed (Graff-Radford and Teruel 2009). However, there is evidence that cluster headache and obstructive sleep apnea are not causal, but rather parallel processes possibly generated in the hypothalamus. The exact role sleep apnea plays in the perpetuation or precipitation of cluster headache is still to be determined. A study showed that 50% of cluster headache patients were blood pressure nocturnal “non-dippers,” a frequency higher than expected (Santos Lasaosa et al 2011). Non-dipper patients displayed higher mean nighttime systolic and diastolic blood pressure. The high incidence of non-dipper pattern in cluster headache and obstructive sleep apnea supports the hypothesis of a relationship between these 2 disorders.

Chronic paroxysmal hemicrania is considered a variant of cluster headache, however, with sufficient individual traits to be listed separately. In this condition, attacks of pain are more frequent, but of shorter duration, than in typical cluster headache, and the therapeutic response to indomethacin is quasi-specific. There is a case report of a patient with headaches meeting the criteria of chronic paroxysmal hemicrania who was fully responsive to indomethacin administration during the first 3 months of treatment (Sarov et al 2006). Further investigations revealed a macroprolactinoma, and headaches stopped after cabergoline treatment. The authors suggested that patients with paroxysmal hemicrania should be investigated for pituitary abnormalities.

The following mechanisms have been implicated in headaches on awakening in patients with sleep apnea syndrome: hypoxemia, hypercapnia, altered cerebral blood flow, excessive neck movements, and sleep disturbance caused by depression. However, the exact mechanism of headache and the relationship between obstructive sleep apnea,
headache, and morning headaches in particular, remain controversial (Provini et al 2006). In a study of 462 patients with obstructive sleep apnea compared to controls, the authors found that the apnea-hypopnea index (AHI) was significantly higher in obstructive apnea patients with morning headache compared to patients without morning headaches (Goksan et al 2009). Morning headache was more frequently reported by women with primary headache history. In the same study morning headache was totally resolved in 90% of patients treated with nasal continuous positive airway pressure.

Based on the regularity of events, the hypnic headache syndrome has been linked to an abnormality of the circadian clock, but scientific proof is lacking. The association with dream content suggests linkage to REM sleep. However, Liang and colleagues showed that hypnic headache occurred equally in both REM and non-REM sleep, and most patients ran an episodic course (Liang et al 2008). The clinical spectrum of hypnic headache has been expanded to include unilateral forms (about 40%, half of which are side-locked), forms with a longer duration (up to 3 hours), and cases with onset in juvenile/adult age (De Simone 2006). The location of pain is frontotemporal in over 40% of cases; headache is throbbing in 38% of cases, dull in 57%, and stabbing in less than 5%. Nausea is reported in 19% of cases; photophobia, phonophobia, or both are present in 6.8%. According to some studies, a history of migraine is common in hypnic headache patients, suggesting that hypnic headache and migraine might share a common pathophysiological predisposition (Ruiz et al 2015). One study was unable to confirm a significant role of melatonin concentration changes in the pathophysiology of hypnic headache, discarding melatonin deficiency as a major factor in the pathophysiology of the disorder (Naegel et al 2016).

Bruxism appears predominantly during stage 2, although occasionally it may be observed in stage REM; its mechanism remains unknown. Headaches associated with bruxism are presumed to be secondary to the muscle activity or the temporomandibular joint stress. There is no satisfactory explanation for the association between childhood migraines and somnambulism.

Of some interest is the report of melatonin-responsive headaches in patients with delayed sleep phase syndrome (Nagtegaal et al 1998). Headaches of an assorted variety were alleviated with melatonin 5 mg at bedtime in 5 of 30 patients who reported headache with delayed sleep phase syndrome. The authors suggest that its effectiveness may be due to the chronobiological action of melatonin.

An abnormal pattern of hypothalamic hormonal secretion was found in patients with chronic migraine (Peres et al 2001a). The authors found in 17 patients with chronic migraine and insomnia a decreased nocturnal prolactin peak, increased cortisol concentrations, a delayed nocturnal melatonin peak, and lower melatonin concentrations, which they interpreted as hypothalamic involvement and chronobiological dysregulation due to insomnia. One study provided direct evidence that simultaneous antagonism on both orexin receptors is able to attenuate trigeminal nociceptive activity, as well as induce an elevation of the threshold for the induction of a cortical spreading depression. These data imply that targeting the hypothalamic orexinergic system may offer an entirely novel mechanism for the preventive treatment of migraine with and without aura (Hoffmann et al 2015). These findings are supported by the results of another study that found significantly lower hypocretin-1 levels in chronic and episodic cluster headache patients compared with controls (Barloese et al 2015).

Investigators searching for a relationship between pineal function in chronic migraine, cluster headache, chronic tension-type headache patients, and controls, found abnormal plasma melatonin curves in chronic tension headache and in cluster migraine patients (Bruera et al 2008). Also, plasma melatonin values in cluster headache patients during the cluster period showed an abnormal pattern.

Sleep deprivation may lower the threshold for pain and increase the risk of headaches. In a study, 24 participants were subjected to 3 days of sleep deprivation (Haack et al 2009). Spontaneous pain, including headache, muscle pain, stomach pain, generalized body pain, and physical discomfort significantly increased by 5 to 14 units on a 100-unit scale during total sleep deprivation, compared to the normal sleep condition. Urinary prostaglandin-E2 metabolite significantly increased by about 30% in total sleep deprivation compared to normal sleep condition. Total sleep deprivation-induced increase in spontaneous pain, in particular headache and muscle pain, was significantly correlated with increase in prostaglandin-E2 metabolite. The authors of the study concluded that activation of the prostaglandin-E2 system is a potential mediator of increased spontaneous pain in response to insufficient sleep.
Epidemiology"

Patients seen in headache clinics report a high prevalence of nocturnal or sleep-related headaches. In a study, 17% of the total headache group reported headaches occurring during the nocturnal or early morning (before final awakening) period. Fifty-five percent of patients in the headache subgroup had a specific sleep disorder identifiable by nocturnal monitoring in a sleep center (Paiva et al 1997). Approximately 20% of migraineurs had excessive daytime somnolence in a population-based sample (Kim et al 2016). Cluster headache is predominantly a nocturnal disorder: 75% of cluster headaches appear between 9 PM and 10 AM, and half of them are associated with REM sleep (Pfaffenrath et al 1986). Cluster headache is associated with a sleep apnea syndrome only in the active cluster episode. Only 1 patient out of 5 showed benefit with respect to cluster headache attack frequency (Evers et al 2014).

The prevalence of sleep apnea headache in patients with obstructive sleep apnea is 12% to 18%, which is higher than morning headache with similar symptomatology in the general population (5% to 8%). Oxygen desaturation alone cannot explain the pathophysiology of sleep apnea headache, and the cause of sleep apnea headache remains to be elucidated (Russell et al 2014). In a study, headache frequency was unrelated to severity of obstructive sleep apnea syndrome, albeit patients with sleep apnea had more headaches than control subjects (Aldrich and Chauncey 1990). In a study of 4759 patients diagnosed with obstructive sleep apnea, the prevalence of tension-type headache was 10.2% among sleep apnea patients and 7.7% among nonapnea patients (p < 0.001). The results suggest that patients with obstructive sleep apnea have a higher likelihood of developing tension-type headache than patients without sleep apnea (Chiu et al 2015).

Children with migraine may have an increased incidence of disturbed sleep and parasomnias (Bruni et al 1997), somnambulism, night terrors, and enuresis. Prolonged deep sleep is a risk factor for the provocation of sleep terrors and somnambulism, as well as for triggering migraine attacks in susceptible patients (Dalessio 1994); these observations may have pathogenetic relevance. Ninety percent of the population grinds their teeth, but only in 5% will bruxism present as a clinical condition. In a study of 887 school-aged children in Spain, the authors found that the population with headaches had a greater number of sleep disorders, mainly insomnia, excessive daytime sleepiness, and parasomnias (TTomás-Vila et al 2009). The authors concluded that it is important to gather information about sleep habits in any child who consults for headache. Interestingly, the prevalence of pain, sleep problems, and fatigue, in addition to headache in boys and girls, increased significantly (p<.05) from 1989 to 2005 in Finland (Luntamo et al 2012). All symptoms were associated with each other and with the child’s psychiatric problems. However, psychiatric problems did not explain the observed increase in the symptom frequencies. Cerminara and colleagues reported 3 children between 7 and 11 years old with features of hypnic headache (Cerminara et al 2011). These cases may expand the clinical spectrum of hypnic headache.

Patients with narcolepsy reported an abundance of headaches in a survey conducted in Germany (Dahmen et al 1999). A group of 68 patients with idiopathic narcolepsy were interviewed for the presence of headaches. Eighty-one percent reported headaches that fit an InternationalHeadache Society diagnosis whereas 54% (64% women, 35% men) had migraine with the full complement of International Headache Society criteria.

In a study of 56 patients with obstructive sleep apnea syndrome compared to 50 patients with insomnia, the authors reported that in patients with obstructive sleep apnea syndrome, headache had most frequently a tension-type pattern and occurred on awakening in 74% of patients (Alberti et al 2005). Morning headache was common in habitual snorers and associated with poor health-related quality of life (Chen et al 2011).

The prevalence of sleep disorders was evaluated in 105 consecutive patients with daily or nearly daily headache and in 102 patients with episodic headache, matched by age, sex, and type of headache at onset (Sancisi et al 2010). Patients with chronic headache showed a high prevalence of insomnia, daytime sleepiness, and snoring with respect to controls (67.7% vs. 39.2%, 36.2% vs. 23.5%, and 48.6% vs. 37.2%, respectively). Forty-five patients with chronic headache (42.9%) had psychiatric comorbidity (anxiety or depressive disorders) versus 27 episodic headache patients (26.5%).

In a probability sample of adults in the United States, a structured interview administered by trained interviewers was used (Lateef et al 2011). Diagnostic criteria for migraine and migraine with aura were based on the International Headache Society classification. The presence or absence of 4 forms of sleep disturbance associated with an insomnia diagnosis was ascertained. The authors found a significant association between frequent severe headache, including migraine with and without aura, and disordered sleep. Adults with headache reported more frequent difficulty initiating
sleep (odds ratio [confidence interval] = 2.0 [1.6-2.5]), difficulty staying asleep (2.5 [2.1-3]), early morning awakening (2.0 [1.7-2.5]), and daytime fatigue (2.6 [2.2-3.2]) compared to the individuals without headache. The authors concluded that adults with severe headache are at a significantly higher risk of suffering from sleep disorders, regardless of specific headache type. Optimal treatment of headache must include investigation for sleep disorders and vice versa.

**Prevention**

Proper sleep hygiene is paramount to aid in the prevention of sleep-related headaches. Bruni and colleagues evaluated the effect of modifying bad sleep habits across several headache parameters in 70 migraineurs with poor sleep hygiene (Bruni et al 1999). They instructed half of the group to improve their sleep hygiene while giving no directions to the other half. Mean duration and frequency of migraine attacks were significantly reduced at follow-up in the group asked to maintain proper sleep hygiene. The authors concluded that treatment through a simple modification of sleep behavior is an alternative approach to the treatment of migraine. Daily administration of preventive therapy is considered when migraine attacks occur more than twice a month or when they are prolonged and refractory to acute therapy. All effective headache medications interact with the serotonergic system and, thus, will likely have some corollary effect on sleep.

Cluster headaches are prevented with avoidance of triggering factors, foremost of which is alcohol consumption. Sleeping late in the morning has been cited as a precipitating factor that should be avoided by patients with cluster headache.

Successful treatment of sleep apnea syndrome with nasal CPAP, bilevel positive airway pressure, or tracheostomy will eliminate associated headaches on awakening.

Episodes of bruxism may be reduced with stress management and are eliminated with diazepam, although the latter may not be a therapeutic option. In a 12-week randomized, double-blind, placebo-controlled, parallel-group study, 60 patients with migraine without aura were randomized to receive memantine (10 mg/day) or placebo for 12 weeks (Noruzzadeh et al 2016). The primary outcome was the monthly attack frequency at week 12 between the 2 groups. The authors found that memantine might be a tolerable and efficacious option for prophylaxis in patients with migraine without aura.

In 1 study of noninvasive vagus nerve stimulation (nVNS), 20 patients with treatment-refractory migraine were enrolled in a 3-month, open-label, prospective observational study (Kinfe et al 2015). The patients received nVNS prophylactically twice daily and acutely as adjunctive therapy for migraine attacks. Outcomes were pain intensity, number of headache days per month, number of migraine attacks per month, number of acutely treated attacks, time to achieve pain relief, and sleep quality. Treatment with nVNS was safe and provided decreases in the frequency, intensity, and duration of migraine attacks. Improvements in sleep quality were also noted.

**Differential diagnosis**

Each headache evaluation should include at least a brief sleep history (Rains and Poceta 2005). Migraine and cluster headaches occurring at night need to be differentiated from other acute severe headaches such as those associated with intracranial brain tumors, ruptured aneurysm, and meningitis. Patients with intracranial tumors may be awakened at night by headache that improves on getting out of bed. Headaches on awakening, as observed in sleep apnea patients, are also seen in patients with severe hypertension, depression, intracranial tumor, muscle contraction headache, alcohol intoxication, and craniofacial sinus disease. Causes for concern are first or worst ever headache, associated neurologic symptoms or signs, progressive worsening of headache over days or weeks, intractable nausea or vomiting, fever, lethargy, confusion, and stiff neck. Hypnic headaches differ from cluster headaches and chronic paroxysmal hemicrania by their lack of unilateral pain with autonomic symptoms and their older age of onset.

**Diagnostic workup**

Neurologic consultation, neuroimaging studies, and lumbar puncture are indicated in patients who exhibit causes for concern. Nocturnal polysomnography is indicated for the study of patients suspected of having sleep apnea disorder or recurrent parasomnias. Videotaping should always be included in the polysomnographic study of parasomnias. Somnambulism and sleep terrors are associated with stage N3 of sleep. Patients with migraine, cluster headache, and
hypnic headache may wake up with an acute attack more frequently during stage REM than during other stages of sleep, and those with cluster headache may suffer the attack at the same time of the night every night. Nocturnal polysomnography in patients with hypnic headache has shown arousal from stage 3 because of headache (Arjona et al 2000), although other authors have found no consistent results (Dodick 2000). Attacks of chronic paroxysmal hemicrania may be so closely linked to REM sleep that they have been termed “REM sleep-locked.” Bruxism occurs in stage N2 of sleep and less commonly in stage REM. The exploding head syndrome appears during nocturnal awakenings.

The use of polysomnography has been recommended in patients complaining of morning and nocturnal headaches (Paiva et al 1995). In a study of 25 patients with headache, Paiva and colleagues found 21 with disturbed sleep. The clinical diagnosis was reassessed after polysomnography in 13 patients due to the finding of obstructive sleep apnea, periodic limb movements, alpha-delta sleep, and insomnia. In a polysomnographic study of 30 migraineurs without aura, Karthik and colleagues found significantly lower sleep efficiency, prolonged sleep-onset latency, reduced NREM sleep, and more awakenings in migraineurs compared to controls (Karthik et al 2013). The authors were unable to detect whether these abnormalities were due to migraine or associated comorbidities.

Clinical evidence strongly supports screening for sleep disorders by headache practitioners. Treating sleep disorders may improve or resolve headache (Rains et al 2008).

Management

Medications used to treat headache disorders may have a considerable impact on sleep physiology (Nesbitt et al 2014). Patients with migraine, cluster headaches, and chronic paroxysmal hemicrania should be instructed in good sleep hygiene and should avoid such potential precipitating factors as sleep deprivation, excessive sleep, stress, trauma, and ingestion of certain idiosyncratic foods including alcohol. Preventive treatment of migraine includes beta-blockers; calcium channel blockers; serotonin receptor antagonists (methysergide, only for use in periods not to exceed 4 weeks) and 5-HT2 antagonists cyproheptadine and methylergonovine; antidepressants that interact with serotoninergic receptors such as tricyclics, MAO inhibitors, and serotonin reuptake inhibitors (fluoxetine and sertraline); anticonvulsants, particularly in children with abnormal EEG; and nonsteroidal anti-inflammatory agents. Sumatriptan, a 5-HT1 selective agonist, administered via subcutaneous injection (6 mg, may repeat after 1 hour, limit 2 injections in 24 hours) is an effective abortive medication for migraine attacks. Other abortive medications include ergotamine derivatives, acetaminophen, corticosteroids, and nonsteroidal anti-inflammatory derivatives. Symptomatic treatment for migraine attacks includes nonsteroidal anti-inflammatory derivatives, mixed barbiturate and analgesics, antiemetics (promethazine 50 mg), and in special circumstances of severity meperidine (50 mg) or codeine sulfate (30 mg). A report of a 2006 European Federation of Neurological Societies task force for the drug treatment of migraine recommends oral nonsteroidal anti-inflammatory drugs and triptans for the acute treatment of migraine attacks (Evers et al 2006). The administration should follow the concept of stratified treatment. Before intake of nonsteroidal anti-inflammatory drugs and triptans, oral metoclopramide or domperidone is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are recommended as first choice drugs. Status migrainosus can be treated with steroids. Prophylaxis of migraine may be exercised with beta blockers (propranolol and metoprolol), flunarizine, valproic acid, and topiramate as drugs of first choice. Second choice drugs for migraine prophylaxis are amitriptyline, naproxen, and bisoprolol.

Cluster headaches are prevented with ergotamine derivatives at bedtime (1 to 3 mg sublingual), amitriptyline (150 mg daily), methysergide (6 to 8 mg daily), prednisone (40 mg daily), and lithium carbonate (initial dose 250 mg). An acute attack may be terminated with inhalation of oxygen. In an open-label study (Khatami et al 2011), 4 patients with chronic cluster headache and disturbed sleep received increasing dosages of sodium oxybate, a compound known to consolidate sleep and to increase slow-wave sleep. Sodium oxybate was effective in immediately reducing the frequency and intensity of cluster headaches in all 4 patients, while improving sleep quality. The authors concluded that sodium oxybate may represent a new treatment option to reduce nocturnal and diurnal pain attacks and improve sleep quality in chronic cluster headache. There is 1 case report describing the efficacy of ramelteon—a melatonin agonist—as a preventive treatment for cluster headaches during sleep (Imai 2016).

Chronic paroxysmal hemicrania responds specifically to indomethacin (50 mg at bedtime or 25 mg 3 times a day). Morning headaches related to sleep apnea syndrome disappear with the effective management of sleep apnea. Dodick and colleagues reported successful prophylaxis of hypnic headaches by drinking coffee at bedtime (2 patients); administration of ergotamine tartrate 0.6 mg, phenobarbital 40 mg, and belladonna 0.2 mg at bedtime (9 patients);
atenolol 25 mg at bedtime (16 patients); and aspirin 325 mg and caffeine 40 mg at bedtime (18 patients) (Dodick et al 1998). Indomethacin 25 mg at bedtime relieved symptoms in 1 case (Ivanez et al 1998), and flunarizine 5 mg at bedtime in 2 cases (Morales-Asin et al 1998). One report reiterates the successful elimination of hypnotic headache with the administration of indomethacin 150 mg daily over a period of 1 month (Bussia et al 2005). Moderate doses of lamotrigine have been reported as an alternative favorable treatment for hypnotic headache (Ouahmane et al 2012). Successful prophylaxis with lithium carbonate has also been reported (Raskin 1988; Dodick et al 1999). Reassurance and administration of clomipramine are curative in most instances of exploding head syndrome. Topiramate may be an alternative method for reducing the intensity of events in exploding head syndrome (Palikh and Vaughn 2010). Bruxism is treated with stress management, a mouth guard, or an intraoral occlusal splint (Holmgren et al 1993). For short-term management, diazepam (5 mg) given at bedtime will reduce the tooth-grinding activity.

The symptoms of postconcussional syndrome may respond to the administration of tricyclic antidepressants. Good to excellent relief of symptoms has also been obtained with the administration of intravenous dihydroergotamine and metoclopramide (McBeath and Nanda 1994). Drug-related headaches tend to be benign and respond to conventional analgesics or disappear gradually with continued use of the drug. If necessary, discontinuation of the offending drug should be recommended, an action generally followed by disappearance of the headache.

Headache patients should be evaluated for the presence of obstructive sleep apnea as treating obstructive sleep apnea may improve headaches in some patients. In a retrospective chart review of all patients referred to an adult neurology clinic for headaches and sent for polysomnography in the span of one year, 82 headache patients were studied (Johnson et al 2013). Females predominated (70 females, 12 males), and the mean age was 45 ± 13 years with a mean body mass index of 32 ± 9. Fifty-two patients (63%) had obstructive sleep apnea. Increasing age, female gender, and chronic migraine without aura were predictive of obstructive sleep apnea. Patients with obstructive sleep apnea who were CPAP adherent (21/27) were more likely to have improvement in headaches than patients intolerant of CPAP (2/6), those who did not use CPAP (8/19), and those who did not have obstructive sleep apnea (16/30) (p = .045). Of the 33 patients who used CPAP, 13 reported improvement in headaches specifically due to CPAP therapy, and 10 additional patients noted benefit in sleep symptoms.

Severely obese migraineurs experienced marked alleviation of headaches after significant weight reduction following bariatric surgery. In a prospective observational study, 24 patients with migraine headaches were assessed before and 6 months after bariatric surgery (Bond et al 2011). Patients were mostly female (88%), middle-aged (mean age 39.3), and severely obese (mean body mass index 46.6) at baseline. The mean number of headache days was reduced from 11.1 ± 10.3 preoperatively to 6.7 ± 8.2 postoperatively (p < 0.05) after a mean weight loss of 49.4%. Reductions in severity were also observed (p < 0.05); the number of patients reporting moderate to severe disability decreased from 12 (50.0%) before surgery to 3 (12.5%) after surgery (p < 0.01).

**Special considerations**

**Pregnancy**

Remissions of migraine attacks and cluster headaches are common during pregnancy. Preventive medications should be discontinued during pregnancy. Ergotamine and its derivatives are to be avoided during pregnancy. On the other hand, migraine headaches and sleep disturbances are common comorbid conditions among pregnant women as noted in a cross-sectional study conducted among 1324 pregnant women. The odds of sleep disturbances were particularly elevated among prepregnancy overweight migraineurs (Qiu et al 2015). Memantine might be advantageous over other antimigraine medications in pregnancy because of tolerability, short duration required for titration, and safety profile (Noruzzadeh et al 2016).

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Headache: 784.0
Migraine: 364

ICD-10:
Headache: R51
Migraine: G43.0

Profile

Age range of presentation

02-05 years
06-12 years
13-18 years
Sex preponderance

male>female, >1:1

Family history

family history may be obtained

Heredity

heredity may be a factor

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

acute severe headache associated with intracranial brain tumors
acute severe headache associated with ruptured aneurysm
acute severe headache associated with meningitis
severe hypertension
depression
muscle contraction headache
alcohol intoxication
craniofacial sinus disease

Other topics to consider

Childhood migraine
Cluster headache
Epidemiology of headache
Hypnic headache
Insomnia
Insufficient sleep syndrome
Migraine
Narcolepsy
Obstructive sleep apnea
Parasomnias
Paroxysmal hemicrania
Sleep bruxism
Sleep disorders
Sleep enuresis
Tension-type headache

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