Chapter 6
Sleep Disorders Comorbidity

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Abstract The common structural and neurotransmitter pathways between headache and sleep accounted for the strict comorbidities between these two conditions, since it is mediated by the structural co-alteration of serotonergic and dopaminergic pathways that affect migraine and sleep.

Both an excess or a lack of sleep could be trigger for a migraine or headache attack, but also sleep could be a relieving factor for headache. Therefore, the link between sleep and headache or migraine is complex and could not be simply explained by the common neurotransmitters alterations. Different comorbid sleep disorders, like insomnia, parasomnias (sleepwalking, sleep terrors, enuresis), restless legs syndrome, periodic limb movements, and narcolepsy, could have distinctive pathogenetic causes. Alteration of sleep architecture, sleep fragmentation or hypoxia linked to sleep apnea are common recognized factors affecting headache or migraine. Often the treatment of a sleep disorder could resolve or improve headache and on the other hand the drugs used for migraine/headache prophylaxis could improve sleep.

Keywords Headache • Migraine • Sleep disorders • Parasomnias • Restless legs syndrome • Periodic limb movements • Sleep apnea • Narcolepsy • Colic

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M.A. Giamberardino, P. Martelletti (eds.), *Comorbidities in Headache Disorders*, Headache,
DOI 10.1007/978-3-319-41454-6_6

6.1 Introduction

Narcolepsy, restless legs syndrome, and sleep deprivation are the sleep pathologies considered among the recognized comorbidities of migraine [21, 150].

Depression and other psychiatric disorders together with pain disorders and stressful life events considered as headache comorbidities [133] are also risk factors or comorbidities for chronic sleep disorders.

Therefore the aim of this chapter is to stress the relevance of sleep in the framework of headache comorbidities.

Sleep represents the only well-documented behavioral state related to the occurrence of some headache syndromes, while headache may cause various degrees of sleep disruption. Different studies have shown a strong association between sleep and headache, which are related in a complex and not well-understood fashion [136].

Clinical observations and experimental data suggest that sleep and headache share common anatomical, physiological, and biochemical substrates.

An excess or lack of sleep [42, 70, 130], a bad quality and inadequate duration, can induce headache. Headache can be the result of abnormal sleep events, such as hypoxia or hypercapnia secondary to obstructive sleep apnea [3].

Headaches are known to occur during sleep, after sleep, and in relationship with various sleep stages [36, 117].

Many chronic headache patients, whatever their type, complain of insufficient and nonrestorative sleep, while sleep is effective in the relief the head pain [11, 46] probably through an autonomic reset [40].

Sleep disorders have been correlated with multiple diseases, but only few of them are linked by neuroanatomical and pathophysiological substrates. Headaches are the most frequent complaint showing this link with sleep disorders [44, 48].

Therefore, sleep disturbance and headache might represent the manifestations of a common underlying pathogenesis leading to migraine symptoms and sleep disturbances [106]. However, the findings are often controversial, and some of the relationships still remain unclear [40, 93, 108].

A model of interaction between headache and sleep has been proposed combining clinical data and experimental evidence [130]. Table 6.1 summarizes available data.

6.2 Pathophysiological Aspects

The pathophysiological links between headache and sleep can be defined and organized in the following aspects:

1. They share common anatomical pathways.
2. Their mechanisms depend on the same neurotransmitters.

Table 6.1 Relations between sleep and headache

Sleep
Trigger factor for headache (excessive, reduced or disrupted, increased deep sleep)
Relieving factor for headache
Cause of headache (e.g., sleep apnea)
Headache
Cause of sleep disruption (e.g., attacks occurring during sleep)
Comorbidity with sleep disorders (parasomnias, restless legs syndrome)
Headache/sleep association
Intrinsic origin (modulation through the same neurotransmitters)
Extrinsic origin (i.e., fibromyalgia syndrome)
Reinforcement (bad sleep hygiene)
Sleep related headache (during or after sleep)
Sleep stage relationship: REM sleep (migraine, cluster); slow-wave sleep (migraine)
Headache/sleep comorbidities
Insomnia
Restless legs syndrome and PLMS
Parasomnias
Narcolepsy
Sleep deprivation
Sleep habits

3. There are common genetic mechanisms.
4. They share chronobiological patterns and dysfunctions.
5. They may be caused by the same behavioral dysfunctions.
6. Early life alterations of sleep can induce headache latter in life.
7. Sleep is a headache trigger.
8. They have a bidirectional impact.
9. Several headache disorders have specific links with sleep dysfunctions.

6.2.1 Common Anatomical Pathways

The structural pathways involve the trigeminal nucleus caudalis in the pons and midbrain and the hypothalamus (emergence and spreading of the head pain), the hypothalamus with its connection to the pineal gland, the noradrenergic locus coeruleus, the antinociceptive system represented by the rostral ventromedial medulla oblongata, the serotonergic raphe nuclei, the noradrenergic locus coeruleus, and the periaqueductal gray (PAG) matter. All these structures are involved in the control of the sleep–wake cycle and in the modulation of pain through the action of the serotonergic and dopaminergic systems [41, 51, 124, 156].

6.2.2 Shared Neurotransmitters

The serotonergic system, in particular, might play an important role in the relationship between headache and sleep.

Serotonergic modulation of the sleep–wake cycle takes place through a multitude of postsynaptic receptors which mediate different or even opposite responses, such as facilitating sleep and inhibiting REM sleep; on the other hand, serotonin is important to the maintenance of behavioral sleep, which again depends on the complex interaction between the serotonergic and other neurotransmitter systems [125].

The direct role of the dopaminergic system in migraine pathogenesis has been linked to a dopaminergic receptor hypersensitivity or a dopaminergic imbalance that could account for increase of awakenings and wake during sleep and/or could lead to a decrease in activity and cortical activation [116]. In fact, individuals susceptible to migraine appear either to have genetic polymorphisms in the dopamine D2 gene, which increases responsiveness to dopamine, or to have defects in tyrosine hydroxylase, which inhibits dopamine metabolism. An imbalance of the dopaminergic system is responsible for some premonitory symptoms of migraine, such as nausea, yawning, and dizziness [96, 125].

Dopamine is also quite relevant in sleep: it is involved in several sleep disorders such as restless legs syndrome (RLS) and periodic leg movements of sleep (PLMS). Parkinson patients have important sleep dysfunctions and daytime sleepiness. Dopamine is involved in the circadian system by acting upon the pineal gland, and sleep deprivation in normal subjects increases dopamine levels in the brain.

6.2.3 Genetic Mechanism

Genetic association has been described between RLS and migraine, which seems to exhibit a polygenic inheritance pattern and at least seven genetic loci have been linked to RLS [21]. Such joint genetic origin is attributed to chromosome 14q21 [129]. In fact, there are occasional pedigrees in which RLS and migraine appear to co-segregate over several generations [87, 141].

6.2.4 Chronobiological Mechanisms

Several findings suggested a role for chronobiological factors in migraine, probably related to a hypothalamic involvement [42]. Clinical observations showed that migraine attacks have a seasonal, menstrual, and circadian timing, suggesting a role of chronobiological mechanisms and their alterations in the disease [5, 137]. It has been shown that migraine attacks exhibited a circadian periodicity with a peak during the first hours of waking (between 4 and 9 AM), a menstrual periodicity with a

peak after the onset of menses, and a weak seasonal periodicity with a mild over-representation during the summer months [56].

Furthermore, migraine patients are more frequently morning- and evening-type subjects than controls [62].

Several studies have shown a decrease in melatonin levels in subjects with migraine and cluster headache and a positive response to its therapeutic use in migraine, cluster, and hypnic headache [1, 14, 22, 28, 31, 32, 89, 90, 98, 101, 102, 113–115, 128, 148, 149, 154].

Peres [115] studied the plasma melatonin nocturnal profile: lower melatonin levels were observed in migraineurs with insomnia when compared with those without insomnia, together with a phase delay in the melatonin peak suggesting a chronobiological dysfunction in insomniac chronic migraineurs.

6.2.5 Induced by Common Behavioral Dysfunctions

Sleep hygiene has been defined as the conditions and practices that promote continuous and effective sleep: these include regularity of bedtime and arise time; conformity of time spent in bed to the time necessary sustained and individually adequate sleep, restriction of beverages, foods, and compounds (which tend to disrupt sleep) before bedtime; and regular exercise, nutrition, and environmental factors so that they enhance, not disturb, restful sleep [105].

In the first study published on sleep hygiene in adolescents with migraine, Bruni et al. [16] instructed 35 children and adolescents to follow directions to improve sleep hygiene, and the patients showed a significant decrease in the mean duration and frequency of migraine attacks, while the severity of the attacks did not change.

In adolescents, headaches are significantly related with sleep deprivation [107], sleep habits, and sleep disorders [17, 49, 50, 109].

The application of sleep hygiene guidelines could represent an alternative approach to the treatment of migraine by correcting an inappropriate sleep behavior, without recurring to pharmacological treatment. Melatonin in migraine might act also as a chronobiotic agent through a sleep hygiene effect [12].

On the other hand, excessive working hours, disruptive work schedules, daily stress, and stressful life events can provoke both headaches and sleep complaints, mainly insomnia.

6.2.6 Early Life Dysfunctions

A structural alteration of neurotransmitter pathways (serotonergic and dopaminergic) might act since the early period of life, predisposing to disorders of the sleep–wake rhythm in infancy and to the development of a headache disorder, as a result of this neurotransmitter imbalance.

Early-onset sleep disorders have been found to be predictive of headache persistence from infancy to childhood: they were reported in 78 % of children with enduring headache vs. 25 % of children showing headache remission [64].

6.2.7 Sleep as a Headache Trigger

Different studies in adults showed that lack of sleep was a most common factor to trigger headache together with emotional stress, physical strain, and particular foods [52].

An epidemiological study on 385 migraineurs and 313 non-migraine headache sufferers demonstrated that the most frequent precipitating factors were fatigue, sleep, stress, food and/or drinks, menstruation, heat/cold/weather, and infections in both groups. Sleep problems, rather than provoking migraine, can be premonitory symptoms similar to mood changes, food cravings, or surges of energy, which can occur many hours before the migraine attack [26].

6.2.8 Bidirectional Impact

The most frequent complaints of headache adult patients are represented by fatigue, tiredness, or sleepiness associated with insomnia [76].

Headache sufferers reported bad sleep more frequently than controls [33] and slept significantly shorter (6.7 h vs. 7.0 h); it took them longer to fall asleep (31.4 versus 21.1 min) and longer to fall back asleep after waking up at night (28.5 versus 14.6 min) [138].

More difficulty at sleep onset, more awakenings, more nocturnal symptoms (hypnagogic startles, restless legs syndrome, pain, respiratory problems, sweating, bruxism), and more awakening symptoms such as non-refreshing sleep, fatigue, paralysis, and daytime somnolence were reported in 75 adult chronic headache patients compared to 50 healthy controls [108].

In a recent study, 28,828 US citizens were scanned for severe headaches and sleep disturbances. Approximately 15.1 % of adults aged 18 years or older reported severe headaches in the past 3 months. Those reporting severe headaches were significantly more likely to have insomnia, excessive sleepiness, recurrent pain, and depression or anxiety symptoms during the preceding 12 months. Approximately 88 % of those with severe headaches also had at least one comorbid medical condition, compared to 67 % of those without severe headaches [140].

Headache also impacts upon sleep: Cluster headache patients and those with hypnic and sleep-related headaches may try not to fall asleep in order to prevent their headaches.

6.2.9 Headaches and Sleep Disorders

6.2.9.1 Insomnia and Headache

Insomnia is a common complaint, and like most headaches, it is more frequent in women. Different recent studies highlighted the strict relation between headache and insomnia. In a study of 50 insomniacs, 24 subjects (48 %) also complained of headache, mostly migraine without aura (37.5 %) or episodic tension-type headache (50 %) [3], but only 10 % had headache upon awakening.

A national survey in the United States recruited 5484 adults; it showed a significant association between frequent and severe headache, including migraine with and without aura, and insomnia, without differences between specific headache subtypes. Adults with headache were more likely than those without headache to report at least one of four insomnia symptoms: difficulty initiating sleep, maintaining sleep, waking up early, and daytime fatigue. Subjects with headache were more than twice as likely to report three or more of these symptoms than those without headache (1.83 % vs. 0.60 %; OR 2.5; CI 2.0–3.1) [88].

A Chinese study showed that the prevalence of DSM-IV insomnia was higher in women with headache than in those without headache (19.9 % vs. 5.3 %; $p < 0.01$). After adjusting for age and menopausal status, women with migraine, tension-type headache, and unspecified headache were significantly more likely than women without headache to report insomnia symptoms of difficulty in initiating and maintaining sleep and waking up early. Women with insomnia had a 4.0-fold increased risk of having headache at least once per week: in particular, a 3.2-fold increased risk of migraine, a 2.3-fold increased risk of tension-type headache, and a 2.2-fold increased risk of headache in general [152].

A population study in Norway showed that subjects with insomnia were significantly more likely, compared to those without insomnia, to suffer from headache in general (17.6 % vs. 11.8 %; OR 1.68; CI 1.58–1.79, $p < 0.001$) and migraine (16.8 % vs. 13.3 %; OR 1.41; CI 1.29–1.55, $p < 0.001$) [73].

A follow-up of the same study reported that, after adjusting for age, gender, and sleep medication, insomnia among headache-free subjects at baseline was associated with a significantly increased risk of headache 11 years later ($p < 0.001$). There was also a significant association between insomnia at baseline and headache frequency at follow-up, specifically for migraine ($p = 0.02$) and tension-type headache ($p < 0.001$) [104].

It is evident that headache and migraine are associated with insomnia, while only severe insomnia is associated with headache or migraine. In addition, it was found that insomnia is a risk factor for headache or migraine onset and for increased headache frequency, specifically for tension headache and migraine.

As insomnia appears to be a risk factor for headache or migraine onset, insomnia patients should probably be routinely evaluated for headache, and, on the other hand, tension headache and migraine patients should probably be routinely treated for insomnia, if present, as part of their overall management [142].

6.2.9.2 Snoring and Obstructive Sleep Apnea Syndrome (OSAS)

There is evidence that sleep-disordered breathing is associated with headaches. Self-reported snoring has been associated with morning and daytime headache [27, 103, 132, 144], and habitual snoring was more frequent in patients with chronic daily headaches (24 %) vs. controls (14 %) [131].

The prevalence of headache in a population of patients with OSAS has been evaluated by different authors [4, 13, 61, 63, 75, 103, 119, 131, 144] and ranged from 32.9 to 58.5 %. However, when evaluating in a headache clinic, the prevalence of OSAS was not different from that in the general population [77].

Guilleminault et al. [65] reported a 36 % incidence of morning headaches in 50 patients with sleep apnea. Dexter [37] reported 11 patients with chronic recurring headaches with a history suggestive of sleep apnea that was confirmed polysomnographically: ten of these patients had sleep apnea and one had mixed sleep apnea. Mathew et al. [97] also reported headache in patients with sleep apnea: 3 out of 18 patients with chronic headaches and 1 out of 4 patients with cluster headache had sleep apnea. Kudrow et al. [86] found a 60 % prevalence of sleep apnea among ten patients with cluster headaches: four of these patients had central apneas and two obstructive apneas.

The clinical presentation is a morning tension-type headache, mainly frontal, frontotemporal, or temporal (38.9 %) in location, tightening or pressing (78.9 %), and mild to moderate (84.2 %) [3]. Chronic headache was seven times more common among subjects with OSAS than in the general population, and treatment of sleep apnea (nCPAP) leads to headache improvement [47].

Several reports showed that migraine attacks in sleep apnea patients occur usually during nighttime or early morning [4, 13, 65]. Subjects with obstructive sleep apnea and other sleep disorders evaluated in a sleep laboratory had a higher headache frequency, mostly morning headaches, compared with healthy subjects [61].

In a population-based cohort study, the authors evaluated the effects of sleep-related breathing disorders (SBDs) on migraine development in patients aged 20 years or more and diagnosed with SBD. The cumulative incidence of migraine was significantly higher in the SBD cohort than in the control cohort. The risk of developing migraine was higher in men than in women with SBD; moreover, the incidence of migraine was higher in patients aged 20–44 years and 45–64 years. The findings indicated increased risk of developing migraine in adults, but not elderly, with SBD [66].

Jensen et al. [77] assessed the frequency of OSA in a population of headache patients. Seventy-five of 903 headache patients reported heavy snoring and episodes of interrupted nocturnal breathing (8 %). Among 43 patients examined with polysomnography (PSG), 14 (1.5 % of the total study population) had an apnea/hypopnea index (AHI) of 5/h or higher. Eleven of the patients reported morning headache. They concluded that OSA's prevalence is not higher than what is reported for the general population but that chronic daily headache appeared to be more frequent in patients with OSA. Idiman et al. [69] did not find a statistically significant relationship between headache and AHI or minimal oxygen saturation. Kallweit et al. [78]

reported that 11 (10.3 %, 8 % male) of 107 consecutive patients with OSA fulfilled diagnostic criteria for migraine (migraine with aura [MA] in four, migraine without aura [MO] in six, and CM in one). They did not find significant differences between patients with or without migraine. After 1 year, however, continuous positive airway pressure (CPAP) treatment was effective for sleep apnea, sleep quality, and migraine. Kristiansen et al. [85] concluded that migraine and OSA are unrelated in the general population. They investigated the relationship between migraine and OSA in a random age- and gender-stratified sample of 40,000 persons aged 20–80 years. Three hundred and seventy-six subjects with high risk and 157 with low risk of sleep apnea aged 30–65 years were identified based on screening questionnaires. They underwent clinical evaluation, a structured headache interview, and PSG. No relationship was found between MO or MA and OSA. This was true for moderate and severe OSA. Greenough et al. [63] found no relationship between the duration of nocturnal hypoxemia and headache complaints in patients with OSA.

Few data are available on the relationship between sleep apnea and migraine in children. Guilleminault et al. first reported that 18 of 50 OSA patients suffered from frontal or diffuse morning headache; afterward, several other reports supported this important relationship [65, 110].

A varied range of symptoms and signs are associated with OSAS in the pediatric population. In children and adolescents with OSAS, the most common clinical manifestation reported is snoring but also obesity, excessive daytime sleepiness, heavy habitual snoring, and neuropsychological disturbances [103]. Morning headaches and poor appetite may also present in OSAS, particularly in school-aged children, and it is one of the Diagnostic Criteria of Pediatric Obstructive Sleep Apnea by the American Academy of Sleep Medicine which may be due to carbon dioxide retention, sleep fragmentation, or gastroesophageal reflux [71].

A polysomnographic study in children with headaches indicated that sleep-disordered breathing was more frequent among children with migraine (56.6 %) and nonspecific headache (54 %) vs. chronic migraine (27 %) [44].

In synthesis, the prevalence of headaches is higher in OSA patients. The data concerning the higher prevalence of OSAS in migraine patients are controversial and point to an inexistent impact upon prevalence.

The association between headache and OSAS is probably based on a combination of factors: hypercarbia, hypoxemia, altered cerebral blood flow, increased intracranial pressure, alterations in sympathetic nerve activity and increases in blood pressure secondary to multiple arousals, and brainstem dysfunction. However, it has been hypothesized that migraine attacks could be secondary to sleep disruption rather than to sleep apnea by itself [142].

These findings revealed a strong relationship between migraine and sleep-disordered breathing, while chronic migraine was associated with more disrupted sleep and tension-type headache with bruxism. It is hypothesized that sleep-disordered breathing may predispose patients to sleep fragmentation, which in turn may exacerbate or aggravate preexisting signs of migraine, because sleep deprivation is known to trigger or worsen migraine attacks [40].

6.2.9.3 Restless Legs Syndrome

Restless legs syndrome (RLS) is commonly represented by an urge to move the legs, accompanied by unpleasant leg sensations, occurring at night, worsened by rest, and improved by movements [155].

There is evidence that restless legs syndrome (RLS) is another condition frequently reported by migraine patients [21]. RLS prevalence in migraine ranged from 8.7 to 39.0 % with no apparent differences based on gender and aura status, while migraine prevalence in RLS ranged from 15.1 to 62.6 % [54].

The first study suggesting an association between RLS and migraine in the pediatric population was conducted by Seidel et al. [134] and assessed the frequency of RLS in children and adolescents with migraine compared to headache-free controls. The authors included two control groups. The first group was recruited from an outpatient clinic of pediatrics and adolescent medicine (group 1). These children and adolescents were exclusively screened at follow-up after recovery from a minor illness and did not suffer from a significant medical, neurological, or psychiatric condition at the time they were included in this study. The second control group was recruited from primary school (group 2); the aim of the study and the objects of the questionnaires were explained to the children and teachers.

In 111 consecutive patients with a sole diagnosis of migraine with or without aura and 73 headache-free controls, the frequency of RLS in migraine patients was significantly higher (22 % vs. 5 % [$p < 0.001$] group 1 and 8 % [$p < 0.001$] group 2 [134]).

A common pathophysiological origin for migraine and RLS has been proposed [21], and a link involving a disturbance of iron metabolism has been considered. A recent study investigated daytime dysfunction in children with RLS and the effects of treatment primarily with iron supplements on RLS symptoms and daytime dysfunction in 25 children with RLS showing that after treatment, participants' daytime function had improved to levels similar to those of controls. Sixteen out of 23 cases were successfully treated primarily with iron supplement [57].

A link between RLS and a dysfunction within the dopaminergic system has also been suggested [21, 54, 155]. It is supported by the rapid improvement of RLS symptoms after treatment with dopaminergic agents. Dopamine is also involved in migraine pathophysiology. Dopaminergic symptoms (DPS) like yawning, irritability, and mood changes as well as nausea and vomiting occurring both during the premonitory and headache phases are present in 47.6 % migraine patients with RLS vs.13.1 % of those without RLS ($p < 0.001$). A further support to a "dopaminergic link" between migraine and RLS is the observation that antiemetics with antidopaminergic properties are effective in aborting migraine attacks [21].

The prevalence of both RLS and periodic limb movements in sleep (PLMS) increases with age. Complaints of morning or daytime headaches are three to five times more frequent in patients with RLS [145]. Fifty patients with severe headaches who qualified for the treatment with dopamine receptor-blocking agents had a prevalence of RLS of 34 %; this group had a higher risk of developing akathisia as a treatment side effect.

A recent study [146] investigated the prevalence, severity, and correlation between sleep quality and RLS in a large population of migraine patients and non-migraine controls as poor sleep presumably triggers migraine attacks. Restless legs syndrome prevalence in migraine was higher than in controls (16.9 % vs. 8.7 %; multivariable-adjusted odds ratio 1.83; 95 % confidence interval 1.18–2.86; $p = 0.008$) and more severe (adjusted severity score 14.5 ± 0.5 vs. 12.0 ± 1.1; $p = 0.036$). Moreover, poorer sleep quality was independently associated with RLS occurrence and RLS severity in migraine patients.

The hypotheses to explain the coexistence of RLS and migraine are based on a common genetic basis and brain structures involved (like the A11 dopaminergic nucleus of the dorsal posterior hypothalamus that lays a crucial role in RLS and trigeminovascular nociception). Furthermore, cerebral dopamine imbalance and altered iron metabolism were implicated; in fact, dopamine antagonists are effective in migraine attacks, and usually iron deficiency is associated with an increase in extracellular dopamine levels and in the changes in dopamine levels with circadian rhythm that could explain the appearance of RLS symptoms at night and the relationship with migraine because of a dopaminergic hyperfunction reached during the day after lower trough levels [96]. On the other hand, sleep deprivation or sleep instabilities caused by RLS could trigger migraine [54].

6.2.9.4 Periodic Limb Movements

There are only two case reports on increased periodic limb movements in adult headache patients: the first was a patient with hypnic headache syndrome [84] and the second was the case of a man with episodic cluster headache who suffered from severe obstructive sleep apnea and periodic limb movements during sleep [112].

To our knowledge, only one study investigated the presence of periodic limb movements in children with migraine [49]. The questionnaire survey showed that migraine children had a higher frequency of difficulty in falling asleep, non-rapid eye movement sleep parasomnias, and sleep-related movement disorders compared with the control group. In the migraine children group, the individuals with PLM pathological index ($PLMI \geq 5$) represent the 26.47 % of the sample and present higher frequency ($p < 0.001$), intensity ($p < 0.001$), duration ($p = 0.006$), and life impairment as scored in the PedMIDAS ($p < 0.001$) of headache and lower efficacy of prophylactic ($p = 0.001$) and acute ($p = 0.006$) pharmacological treatment than migraine children without PLM pathological index. These findings suggest that PLMS might influence the clinical presentation of migraine, increasing its severity, frequency, and all disabling aspects and also affecting treatment efficacy.

6.2.9.5 Narcolepsy

Narcolepsy is a rare neurological condition characterized by persistent, excessive daytime sleepiness, and generally it is underdiagnosed causing serious problems in patients.

Narcolepsy is considered as a comorbidity of migraine [150], but the association between narcolepsy and migraine is a matter of debate. The German Migraine and Headache Society Study Group [83] reported a similar prevalence of migraine in narcoleptics (21.9 %) and controls (19.8 %).

In this case control study of 96 narcoleptic patients, headache fulfilling the criteria for tension-type headache was significantly more often reported by narcolepsy patients than by the control group (60.3 % vs. 40.7 %) [83].

In another study, migraine prevalence had twofold to fourfold increase in the narcoleptic patients and amounted to 44.4 % in women and 28.3 % in men [34]. The onset of narcolepsy symptoms was 12.3 years before the onset of migraine symptoms. The increased prevalence of migraine was not due to pharmacological treatment for narcolepsy and did not depend on the severity of the narcolepsy symptoms [34].

No studies are available on the prevalence of migraine in children and adolescents with narcolepsy; headache has often been reported as a side effect of treatment in children with narcolepsy.

The relations between narcolepsy and migraine could be mediated by the orexinergic neurons of the posterior hypothalamus that are involved both in inhibition of analgesia and in narcolepsy. Dysfunctional hypothalamic activity might contribute to both altered REM function and altered pain processing via orexinergic neurons [91, 114].

6.2.9.6 Nocturnal Enuresis

Several studies also demonstrated a significant relationship between migraine and nocturnal enuresis. A study highlighted a strong correlation between the clinical history of nocturnal enuresis and the diagnosis of migraine, hypothesizing that nocturnal enuresis is a precursor of migraine and a migraine comorbid condition [92].

The presence of enuresis in migraine children has been previously incidentally reported in earlier studies [6, 55].

Patients with episodic migraine (EM) or chronic migraine (CM) had significantly more often a history of nocturnal enuresis vs. the control group (CG.12 %, EM.41 %, CM.49 %). A common pathophysiological substrate in the hypothalamus could explain this comorbidity through the inhibition of vasopressin secretion that leads to increased urinary frequency during the attack of migraine [111]. Recently, Carotenuto et al. [23] proposed that nocturnal enuresis and migraine could be linked to a dysfunction of the arousal system with primary nocturnal enuresis being considered as a migraine equivalent.

6.3 Specific Sleep Disturbances in Children

Children who suffer from headache have usually a high rate of sleep difficulties, including insufficient sleep, cosleeping, difficulties in falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares, and fatigue during the day [8, 15, 20,

67, 99]. Different surveys in large pediatric populations have confirmed the strong association between headache and different sleep disorders, such as parasomnias, insomnia, sleep breathing disorders, and daytime sleepiness [2, 8, 10, 15, 94, 99].

The first survey on a pediatric population involving 283 headache sufferers, aged 5.0–14.3 years, confirmed the strong association between headache and different sleep disorders [15]: 164 with migraine (141 without aura and 23 with aura) and 119 with tension-type headache (84 episodic tension-type headache and 35 chronic tension-type headache), compared to an age-matched healthy control group.

Sleep duration and sleep latency: migraine and tension-type headache children presented a shorter sleep duration and a sleep latency >30 min. They also showed a higher prevalence of difficulty to fall asleep and of fears or anxiety when falling asleep. Headache children had a more interrupted sleep, with more than two awakenings per night.

Parasomnias: Sleeptalking, bruxism, and frightening dreams were more common in children with migraine, as reported in adults, especially for bruxism [25, 53, 143]. A higher frequency of sleepwalking was found in migraine with aura (13.04 %) confirming data reported in children and adults [7, 59, 121].

Sleep breathing disorders were more frequent in subjects with migraine vs. controls, while tension-type headache failed to show differences, confirming data already reported in children and in adults [8, 123].

Morning symptoms and daytime sleepiness: both groups of subjects with migraine (35.4 %) and tension-type headache (30.3 %) presented more restless sleep than controls (19.7 %); daytime sleepiness affected both headache groups in a higher percentage with respect to controls (12.2 % in migraine; 10.9 % in tension-type; 4.5 % in controls) and represented a worsening factor for the quality of life.

Twenty out of 283 (7.77 %) subjects presented recurrent nocturnal headache attacks and reported more sleep disorders than patients with diurnal attacks. The occurrence of nocturnal headache attacks deeply modifies the sleep pattern and affects the occurrence of night symptoms, confirming the involvement of common pathways in the pathogenesis of both conditions.

An older study evaluating the efficacy of L-5-hydroxytriptophan in 48 children with headache had reported the association of primary headache with sleep disorders: night waking (41.7 %), difficulty in falling asleep (20.8 %), sleep terrors and nightmares (14.6 %), enuresis (8.3 %), and somnambulism (6.3 %) [35].

More recent studies confirmed that children with migraine have an increased prevalence of sleep disturbances, such as bedtime resistance, insufficient and interrupted sleep, sleep-disordered breathing, disorders of arousal, sweating during sleep, difficulty waking up in the morning, and daytime sleepiness [49, 50, 127, 135].

Another study showed that headache characteristics independently predicted sleep anxiety ($p < 0.05$), parasomnias ($p < 0.03$), bedtime resistance ($p < 0.03$), sleepwalking ($p < 0.03$), and bruxism ($p < 0.01$); more specifically, the frequency of migraine predicted parasomnias, while duration of migraine predicted sleep anxiety and bedtime resistance. In this study, again a high rate of sleep disturbances in children, sleeping too little (42 %), bruxism (29 %), cosleeping with parents (25 %), and snoring (23 %), has been reported [99].

Other authors demonstrated that migraine without aura is a risk factor for disorders of initiating and maintaining sleep and chronic tension-type headache for sleep breathing disorders and excessive somnolence [24].

Snoring, parasomnias, sweating during sleep, and daytime sleepiness were more common among children with migraine compared with non-migraine and no headache groups with the odds ratio ranging from 1.97 to 2.17 for habitual snoring and daytime sleepiness [72].

Not all studies were in complete agreement; a recent investigation confirmed the higher prevalence of excessive daytime sleepiness, narcolepsy, and insomnia in children with headaches but not of sleep apnea, restlessness, and parasomnias [94].

6.3.1 Colic

Excessive crying in an otherwise healthy infant is commonly recognized as infant colic, affecting about 5–19 % of the babies. This condition of inconsolable crying in the evening increases in the first weeks of life and tapers off generally by 3–4 months of age [95].

Colicky infants are considered to be candidates for sleep disorders, and some reports revealed an association between infantile colic and migraine [74, 79].

The prevalence of colics in children with migraine is higher than in the control population: Bruni et al. [15] reported a positive history of colic in 38.4 % of subjects with migraine, significantly higher than controls (26.9 %) and subjects with tensive headache (25.2 %). This was further supported by another study showing a positive history of colic in children with migraine (52 % vs. 20 % in controls) [127].

A recent study on 208 consecutive migraine children aged 6–18 years reported infantile colic in 72.6 % vs. 26.5 % of children without migraine [74]. On the other hand, children with tension-type headache (TTH) showed a similar nonsignificant prevalence (35 % vs. 26.5 %), confirming that only migraine is linked with colic.

Colic is a common cause of inconsolable crying and pain in childhood; these two symptoms, in some genetically predisposed infants, could represent a form of infantile migraine with age-specific expression [79].

A case report of a colicky infant with irritability, head slapping with the hands, upper eyelid retraction, and family history of migraine suggested that the excessive crying may have resulted from headache or represent an abdominal migraine variant [74]. This hypothesis has been corroborated by the improvement of colic after the start of migraine therapy (cyproheptadine).

A recent meta-analysis showed that infant colic was associated with increased odds of migraine (OR 5.6, 95 % CI 3.3–9.5) [58]. The ICHD-III in the appendix included infant colic among the episodic syndromes that may be associated with migraine. If infant colic is a childhood periodic syndrome or a migrainous phenomenon, colicky infants could have an increased sensitivity to stimuli due to shared migraine genes. Further, the presence in the evening could be explained by the circadian biology and the fact that colic resolves around age 3 months linked to the

mature pattern of rhythmic excretion of endogenous melatonin [82]. Alternatively, it is possible that the association between infant colic and migraine is due to a shared genetic predisposition to both disorders, rather than infant colic being an early life expression of migraine genetics per se [58].

6.4 Polysomnographic Studies in Headaches

Several polysomnographic studies analyzed the sleep organization in headache and did not find any peculiar characteristics of sleep architecture in the adult population except for the strict relationship of some particular subgroups with specific sleep stages: (a) migraine attacks seem to be linked to REM stages and are associated with a large amount of deep sleep [36, 38]; (b) cluster headache is triggered by REM and NREM sleep particularly stage II [117]; and (c) chronic paroxysmal hemicrania is associated with a reduction of total sleep time and of REM phase, with an increase of awakenings during REM [80].

Headache is the presenting symptom of several sleep disorders that could be therefore misdiagnosed; Paiva et al. [106] demonstrated that, in several cases of adult migraine, after a polysomnographic study, the diagnosis was changed in half of the patients, and the treatment of the underlying clinical condition improved greatly the headache symptom. Among the 25 patients, 13 were misdiagnosed as headache: after the polysomnographic study, the diagnosis was changed in periodic limb movement of sleep in four cases, in fibromyalgia syndrome in six cases, and in obstructive sleep apnea syndrome in three cases.

In adults with migraine, the polysomnographic recording in attack-free periods showed a normal sleep pattern and muscular (EMG) activity in spite of a clear increase in REM sleep duration and latency [45]. Adult migraineurs showed, the day before the crisis, a decreased number of arousals, lower REM density and alpha power, suggesting a decrease in cortical activation [60]. In line with these findings, a decreased EEG complexity was observed in the first two NREM cycles in patients with spontaneous nocturnal attacks [139]. On the other hand, patients with tension-type headaches had persistently poor sleep with reduced sleep efficiency and slow-wave sleep [45].

6.4.1 Migraine

The first polysomnographic study of patients with sleep-related headache showed that awakening-related migraine attacks were associated with REM sleep in all patients: six awakenings from REM sleep; one within 3 min of the completion of a REM period; and one on awakening 9 min following the termination of a REM period [36]. The prevalence of REM-related attacks could be linked to the chrono-biology of migraine since the peak time of attack onset (4–9 AM) is during the hours of REM maximal representation [56]. However, even in a different sleep schedule (7 h sleep shift), the attacks continued to occur during REM sleep (even if

during daytime) demonstrating that migraine was related to sleep rather than to circadian rhythms [39].

Some relationships with NREM sleep have also been found: headache-related awakening occurred from non-REM sleep in two out of three patients with nocturnal headache [30].

Since the reduction of total sleep time and depth of sleep through sleep-rationing was effective in preventing migraine attacks it could be expected that migraine is somewhat related with NREM slow wave sleep (SWS). Dexter [38] confirmed this hypothesis showing that the morning arousals with headache were associated with sleep periods which had large amounts of SWS and REM sleep.

To our knowledge, only one polysomnographic study has been published on children with headaches [147]. This study reported the analysis of polysomnographic findings of 90 children with migraine (60), chronic migraine (11), tension headache (6), and nonspecific headache (13). Sleep-disordered breathing was more frequent among children with migraine (56.6 %) and nonspecific headache (54 %) vs. chronic migraine (27 %). Tension headache was not associated with sleep-disordered breathing. Fifty percent of children with tension headache manifested bruxism vs. 2.4 % of children with non-tension headache. Severe migraine and chronic migraine were associated with shorter sleep time, longer sleep latency, and shorter rapid eye movement and slow-wave sleep.

This study supports the notion that the evaluation of headache in children and adolescents should include an assessment of sleep disturbances and a polysomnographic analysis to confirm certain treatable sleep disorders.

The evaluation of the whole sleep cycle in children and adolescents has also been carried out with actigraphic studies showing that children and adolescents with headache had a poorer sleep quality than controls, with excessive daytime sleepiness, less time spent in quiet motionless sleep, and waking significantly earlier in the morning [19]. A previous study showed that during the interictal period, sleep parameters of children suffering from migraine did not differ from those of controls, but in the night preceding the migraine attack, there was a decrease in nocturnal motor activity, indicating a decrease in cortical activation during the sleep period preceding migraine attacks [18].

6.4.2 Cluster Headache and Chronic Paroxysmal Hemicrania

The description of Wolfe [151] of cluster headache (CH) attacks during sleep, in which patients jump out of the bed before being fully awake, suggested that there was a concurrent presence of a disorder of arousal that preceded or was the consequence of the pain attack. The onset of the nocturnal attacks in cluster headache was either from REM sleep [36] or NREM sleep [117].

Recently, it has been hypothesized that CH could be triggered in some cases by sleep-disordered breathing (SBD) that predicted the occurrence of CH in the first half of the night [29]. Consequently, in most cases of cluster headache, the treatment of the sleep apnea either with surgical interventions or with continuous

positive airway pressure solved or greatly improved the head pain [153]. An old report showed efficacy of melatonin as prophylactic agent in CH [122].

Chronic paroxysmal hemicrania is characterized by frequent nocturnal arousals with pain that occurs mainly from REM sleep and by marked fragmentation of sleep with an excessive number of sleep-stage shifts, a reduction of total sleep time and of REM [80]. This fragmentation of sleep is similar to what is seen in chronic cluster headache.

6.4.3 Hypnic Headache Syndrome

First described by Raskin in 1988, this is a rare recurrent, benign headache disorder occurring exclusively during sleep and in older subjects [126]. The common symptom is regular awakening from nocturnal sleep caused by headache attacks lasting 30–60 min. Recent polysomnographic studies of this syndrome showed conflicting results with a more consistent association with REM sleep in three cases [43] and with stage 3NREM in one case [100].

6.5 Conclusions

Several researches showed the existence of common structural and neurotransmitter pathways between headache and sleep and demonstrated that the pathogenesis of this comorbidity is linked to a structural co-alteration of serotonergic and dopaminergic pathways that affect migraine and sleep.

In the last few years, several studies converged in demonstrating that the link between sleep, headache, and migraine is complex. Comorbidities include insomnia, parasomnias (sleepwalking, sleep terrors, enuresis), RLS, PLMS, narcolepsy, and sleep deprivation. All these sleep disorders together with sleep habits/sleep hygiene represent comorbid, predisposing, predictive, or even prognostic features. In young children, colic should be considered as a putative comorbid symptom of migraine.

It is important for the clinicians to perform the clinical evaluation of headache with a careful analysis of sleep habits and patterns and the evaluation of the presence of sleep disturbances to adequately treat these conditions.

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