Comorbidities of sleep disorders in childhood and adolescence: focus on migraine

Claudia Dosi, Assia Riccioni, Martina della Corte, Luana Novelli, Raffaele Ferri, Oliviero Bruni

Abstract: The correlation and/or comorbidity between sleep disorders and headache has been reported in numerous studies, but the exact nature of the association between headache, disordered sleep, and underlying mechanisms remains poorly understood. The bidirectional association between sleep and headache is mediated by a temporal link (headache occurs during sleep, after sleep, and in relationship with sleep stages), by a quantitative relationship (excess, lack, bad quality, short duration of sleep may trigger headache), and by a reciprocal connection (headache may cause sleep disruption and may be associated with several sleep disturbances). This association is most evident for primary headache disorders, especially in childhood. A congenital alteration of neurotransmitter pathways (serotonergic and dopaminergic) might predispose individuals to both disorders, presenting as sleep–wake rhythm disorder in infancy or as headache disorder later in childhood, as result of this neurotransmitter imbalance. Clinicians should be aware that a complete clinical evaluation of childhood headache includes a careful sleep history, taking into account that the treatment of sleep disturbances could lead to an improvement of headache symptoms and vice versa.

Keywords: sleep, headache, migraine, childhood, adolescence

Introduction

Different scientific reports in the literature have suggested the existence of a correlation and/or comorbidity between sleep disorders and headache, related to common pathophysiological substrates.

An old report of a child with sleep apnea at the end of the nineteenth century by Hill raised the problem of a possible association between headache and sleep-disordered breathing with a relevant passage stating that: “The stupid-looking lazy child who frequently suffers from headache at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes up with a dry mouth in the morning, is well worthy of the solicitous attention of the school medical officer.” However, a clear pathogenetic explanation of this association was not attempted, and presumably it was an example of the “Headache attributed to disorder of homeostasis and linked to the hypercapnia and hypercarbia,” coded as ICHD 10, ICD10 G44.882, in the International Classification of Headache Disorders (ICHD) 2004. Since then, several aspects of the comorbidity between sleep and headache have been investigated and confirmed by the medical literature.

However, the exact nature and magnitude of the association between headache, disordered sleep, and the underlying mechanisms remain poorly understood. It is known that sleep is related to the occurrence of some headache syndromes, while
headache may cause various degrees of sleep disruption and seems to be associated with several sleep disturbances, either in adults or children.\textsuperscript{7,8}

Headache episodes are known to occur during sleep, after sleep, and in relationship with various sleep stages, and on the other hand an excess or lack of sleep or bad quality or inadequate duration of sleep can trigger headache.\textsuperscript{9,10}

Nocturnal migraine attacks are typical effects of sleep disruption, and conversely primary headaches may emerge during nocturnal sleep time, causing sleep disruption.\textsuperscript{5,11}

\textbf{Incidence and prevalence of sleep disorders in headache and migraine}

Both sleep disturbances and headache disorders are widespread health problems during childhood: the aggregate weighted rate of definite migraine in children is 10.1\%, while approximately 25\% of children have experienced at least one type of sleep problem.\textsuperscript{12,13}

Even though several studies have demonstrated a high prevalence of sleep disorders in subjects with headache, they cannot be seen as a comorbid or causative factor for headache.\textsuperscript{14} While patients complain about their sleep disorders, these manifestations are usually considered as “common insomnia” of psychological origin and tend to be considered as not relevant by physicians.\textsuperscript{5,15,16}

In children, the perception of disturbed sleep is missed or underestimated, and it is generally easier for a child to refer to a headache than poor sleep quality. Therefore, the symptom “headache” in children has to be evaluated from different points of view, including an accurate evaluation of sleep behaviors and disturbances.

In general, the relationship between headache and sleep disorders might be mediated by pain: a large community study on 622 children and adolescents with pain (60\% with headache) reported that the most common complaints caused by pain were sleep disturbances (53.6\%), followed by the inability to pursue hobbies (53.3\%), eating problems (51.1\%), and absence from school (48.8\%). Moreover, one of the most frequent self-perceived subjective triggers of pain was the lack of sleep.\textsuperscript{17}

Children who suffer from headache have usually a high rate of sleep difficulties, including insufficient sleep, cosleeping, difficulties falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares, and fatigue during the day.\textsuperscript{5,7} 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.\textsuperscript{18-20}

The first survey on a pediatric population confirmed the strong association between headache and different sleep disorders.\textsuperscript{18} It was a questionnaire-based study involving 283 headache sufferers (144 male, 139 female) aged 5.0–14.3 years: 164 with migraine (M) headache (141 without aura and 23 with aura) and 119 with tension-type (T) headache (84 episodic tension-type headache and 35 chronic tension-type headache), compared to an age-matched healthy control (C) group. Significant differences between headache and controls were found:

1. Sleep duration and sleep latency: children with migraine and tension-type headache presented shorter sleep duration (duration <8 hours in about 18\% of children with headache vs 9.6\% of controls) and a sleep latency >30 minutes in 13.4\% vs 6.6\%.

2. Bedtime problems: children with headache showed a higher prevalence of difficulty to get asleep (M = 20.1\%, T = 17.6\%, C = 8.9\%) and of fears or anxiety when falling asleep (M = 30.5\%, T = 22.7\%, C = 8.2\%).

3. Night awakenings: subjects with headache showed a more interrupted sleep, with more than two awakenings per night in about 13\% of the headache group vs 6.83\% of controls.

4. Parasomnias: sleep talking, bruxism, and reports of frightening dreams were the items in which children with migraine were significantly different from controls, while no differences were observed regarding the prevalence of sleepwalking, bed-wetting, or sleep terrors (Table 1).\textsuperscript{6,7} Analyzing the migraine subgroups, a higher frequency of sleepwalking was found in migraine with aura (13.04\%) vs migraine without aura (2.84\%) and vs controls (3.14\%).

5. Sleep-breathing disorders: sleep-breathing problems were more frequent in subjects with migraine vs controls, while tension-type headache failed to show differences (Table 2).\textsuperscript{6,7} Confirming data already reported in children and in adults.\textsuperscript{21,22}

6. Morning symptoms and daytime sleepiness: both groups of subjects with migraine (35.37\%) and tension-type headache (30.25\%) presented more restless sleep than controls (19.71\%); daytime sleepiness affected both headache groups in a higher percentage with respect to controls (12.20\% in M, 10.92\% in T, 4.48\% in C), and represented a worsening factor for quality of life.

Although no significant differences were found between the migraine and headache groups, the subjects with migraine tended to have the most “disturbed sleep” with a greater prevalence of nocturnal symptoms, such as sleep-breathing disorders and some parasomnias.
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.

In the same study, subjects with migraine reported a higher prevalence of sleep disturbances in parents, sleep disturbances in infancy, and colics, as well as an elevated level of familiarity for headache, showing that a genetic link might be present between migraine and disturbed sleep and indicating that the common neurobiological substrate might act from the beginning of life and/or that a comorbidity exists between these two disorders. This hereditary connection was not sufficiently supported in subjects with tension-type headache.

After this pioneering study, other studies confirmed the strong association between headache and such sleep disorders as parasomnias, insomnia, snoring, sleep apnea, and daytime sleepiness, reporting a general prevalence of sleep disturbances in 25%–40% of children and adolescents with migraine.\(^{23,24}\)

A subsequent study demonstrated a specific comorbidity between these two conditions, showing in a variable range sleep-time reduction (42%), bruxism (29%), and snoring (23%) in a group of 118 patients.\(^{19}\) Looking at the different migraine types, snoring, parasomnias, sweating during sleep, and daytime sleepiness were more common among children with migraine, compared with nonmigraine and no-headache groups,\(^{25}\) while schoolchildren with migraine without aura had a higher prevalence of sleep-disorder symptoms: disorders of initiating and maintaining sleep (37.11% of migraine without aura vs 9.17% of controls), and disorders of arousal (59.32% of migraine without aura vs 10.15% of controls).\(^{26}\)

On the contrary, only one study failed to corroborate the higher prevalence of symptoms of sleep apnea, restlessness, and parasomnias reported in the previous studies, but confirmed the presence of excessive daytime sleepiness, narcolepsy, and insomnia in children with headaches.\(^{27-29}\)

Carotenuto et al showed that migraine without aura is a sensitive risk factor for disorders of initiating and maintaining sleep and chronic tension-type headache for sleep-breathing disorders, but headache disorder is a cumulative risk factor for disorders of excessive somnolence.\(^{30}\)

It has also been demonstrated that frequency and duration of migraine headaches predicted specific sleep disturbances, such as sleep anxiety, parasomnias, and bedtime resistance. Consequently, head pain might be the consequence of a subtle sleep disorder not diagnosed or of bad sleep habits.\(^{19}\)

Pakalnis et al\(^{11}\) recently reported a significant association between sleep and emotional disorders and migraine severity, revealing that patients with chronic migraine had increased daytime sleepiness and dysthymia compared with teenagers with episodic migraine. Specifically, headache patients compared with controls had worse pediatric sleep questionnaire total score, more morning headaches, and more sleepiness. The child sleep habits questionnaire (CSHQ) revealed that the headache group had more daytime sleepiness, night awakenings, sleep-onset delay, parasomnias, and total questionnaire score compared with controls. The same authors also reported no association between serotonin levels and sleep abnormalities or emotional rating scales, while increased caffeine intake was related to sleep and depressive complaints.

According to Pakalnis et al,\(^{31}\) a recent study reported a significant association of primary headaches in children with anxiety and depression, as in adults, while no significant association was found with asthma and allergic disorders, convulsive episodes, sleep disorders, or increased body weight.\(^{32}\)
Comorbidity of early sleep problems and migraine

Sleep problems during infancy can be good predictors for the development of headache. In particular, 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. Further, early sleep disorders have been related to psychiatric comorbidity and involved in the endurance of headache in childhood and adolescence: an 8-year follow-up study found that the most frequent comorbid disorders at the onset of headache were sleep disorders (12%) followed by anxiety (11%); of the nine patients with sleep disorders as comorbid factor at the onset of headache, six had enduring headache and three were headache-free at follow-up.33

Colicky infants are considered to be candidates for sleep disorders, and some reports have shown a relationship also with migraine.34,35 It is known that infantile colic is a periodic behavior in infants and a common cause of crying and pain in childhood; these two symptoms, in some genetically predisposed infants, could represent a form of infantile migraine with age-specific expression.34 The prevalence of colics in children with migraine is higher than in the control population: Bruni et al18 reported a positive history of colic in 38.4% of subjects with migraine, which was significantly higher than controls (26.9%) and subjects with tensive headache (25.2%). This was further supported by another study showing an increased positive history of colic in children with migraine (52% vs 20% in controls).34 Katerji and Painter35 reported a case of a colicky infant with irritability, head-slapping with the hands, upper-eyelid retraction, and family history of migraine, suggesting that the excessive crying may have resulted from headache or represent an abdominal migraine variant. This finding has been corroborated by the improvement of colic after the start of migraine therapy (cyproheptadine).

In addition, hyper-reactivity syndrome during infancy (often associated with night awakenings and falling asleep difficulties) has been reported as a risk and predisposing factor for migraine.36,37

It is therefore possible that the same pathogenetic mechanism underlying headache or migraine and sleep might play a role from early life, supporting the hypothesis of a common intrinsic origin.

Circadian rhythms, sleep hygiene, and headache

Headache has been described as being related to biological cycles, and there is evidence of a relationship of different headache syndromes with a variety of cyclic phenomena. Despite this, few studies have focused on the sleep–wake cycle and on the circadian aspects.

Migraine attacks show different periodicities: (1) a circadian periodicity of migraine attacks, with an overrepresentation during the waking hours (between 4 am and 9 am); (2) a menstrual periodicity, with a peak after the onset of menses; and (3) a weak seasonal periodicity, with a mild overrepresentation during summer.38

Several findings suggest a role of chronobiological factors in migraine, probably related to hypothalamic involvement.11,39 An indirect demonstration of the involvement of the circadian rhythm is the report of five patients with headache with associated delayed sleep-phase syndrome successfully treated with melatonin, which with its chronobiological action synchronizes the patients biological clock and their lifestyle.40 This finding supports the hypothesis that melatonin has a "sleep-hygiene effect," in accordance with the migraine improvement reported in children and adolescents after the application of sleep-hygiene guidelines.41

Melatonin is implicated in the pathogenesis of migraine, menstrual migraine, cyclic migraine, and chronic migraine, and it might also play a role in migraine comorbid disorders, in particular depression and insomnia. Melatonin is linked to the pathophysiology of headache, because of its anti-inflammatory effect, toxic free-radical scavenging, reduction of proinflammatory cytokine upregulation, nitric oxide synthase activity and dopamine-release inhibition, membrane stabilization, gamma-aminobutyric acid and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation, and the similarity of its chemical structure to that of indomethacin.42

Different studies have shown a decrease of melatonin levels in subjects with migraine and cluster headache and a positive response to the administration of melatonin in migraine, cluster, and hypnic headache.42-57 Peres42 studied the plasma melatonin nocturnal profile: lowered melatonin levels were observed in patients with insomnia compared with those without insomnia, and a phase delay in the melatonin peak was observed in patients vs controls, suggesting a chronobiological dysfunction in chronic migraineurs.
Miano et al\textsuperscript{59} administered melatonin to 22 children with headache (13 had recurrent migraine without aura, one with aura, and eight had chronic tension-type headache), showing a decrease in the number of the headache attacks in 14 patients.

Melatonin in migraine might act also as a chronobiotic agent through a sleep-hygiene effect. Sleep hygiene has been defined as the conditions and practices that promote continuous and effective sleep: these include regularity of bedtime and rise time; conformity of time spent in bed to the time necessary for 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 rather than disturb restful sleep. In the first study published on sleep hygiene in adolescents with migraine, Bruni et al\textsuperscript{61} instructed 35 children and adolescents to follow directions to improve sleep hygiene, and patients showed a significant decrease in the mean duration and frequency of migraine attacks, while the severity of the attacks did not change.

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.

The evaluation of the whole sleep cycle in children and adolescents has been carried out in actigraphic studies showing that sleep quality of children and adolescents with headache was poorer than that of controls. This study reported excessive daytime sleepiness, less time spent in quiet, motionless sleep, and waking significantly earlier in the morning. 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.

The preference for morning or evening activity patterns is believed to contribute to interindividual differences in the timing of circadian rhythms. The morning/evening preference might be considered as a continuum between two extremes: morning types (larks) and evening types (owls), but a consistent shift toward “eveningness” has been demonstrated during adolescent development. Children and adolescents with headache show a higher tendency to the eveningness circadian type.\textsuperscript{61,62}

A previous study on the circadian timing of attacks in adult migraineurs showed a preferential timing for occurrence of migraine attacks during the night and early morning hours in a relevant percentage of patients. This study confirmed the hypothesis of an impairment of chronobiological rhythms occurring in migraine together with an alteration in melatonin secretion.\textsuperscript{63}

### Sleep as a trigger and relieving factor for headache

Different studies have reported that sleep problems were the most frequent causes of headache, followed by stress, family problems, and peers,\textsuperscript{54,64} and the lack of sleep was identified as a trigger after certain weather conditions, illness, sports and physical activity, and anger.\textsuperscript{17}

Bruni et al\textsuperscript{67} reported that in a nonclinical group of adolescents with headache, the most frequent triggering factor for headache referred to by adolescents was “a bad sleep” (32.2%), followed by emotional distress (27.8%). On the other hand, clinical studies have demonstrated that sleep, either spontaneous or induced by hypnotics, is efficacious in relieving headache or even terminating the attacks in headache sufferers.\textsuperscript{68,69} Falling asleep during attacks is significantly more frequent in patients younger than 8 years of age than in older children, and in these children there is a higher resolution of attacks with sleep.\textsuperscript{70}

However, the power of sleep in terminating the attack is counterbalanced by its ability to precipitate the attack. Although sleep was more commonly referred to as a relieving factor for migraine (70%), migraine attacks were also precipitated by sleep deprivation in 24% and by sleep excess in 6% of cases.\textsuperscript{71}

It has been hypothesized that the depth of sleep might be responsible for the migraine attack, and the use of a technique named “sleep rationing” (consisting of the reduction of total sleep time and of relaxed sleep and practically leading to a reduction of rapid-eye-movement sleep), was successful in reducing both the intensity and severity of the migraine attacks.\textsuperscript{72}

### Polysomnographic studies

Only a few polysomnographic studies have analyzed sleep architecture in children with headache. Guidetti et al\textsuperscript{73} found that the main feature of sleep organization in children with migraine was represented by a high degree of sleep instability, as demonstrated by the increased number of stage shifts and movement time. The description by Paiva et al\textsuperscript{14} of changing diagnosis in several adults with headache after a polysomnographic study (periodic limb movements during sleep, fibromyalgia syndrome, and obstructive sleep apnea syndrome) raised the possibility of the presence of similar conditions in pediatric patients.
These results are in agreement with a more recent study by Vendrame et al.,\textsuperscript{75} who analyzed the polysomnographic features of 90 children manifesting headaches (including migraine headache, chronic migraine headache, tension headache, and nonspecific headache) and complaints of sleep problems. Children with migraine headache and chronic migraine headache were more frequently affected by sleep-disordered breathing than children with tension headache, indicating a strong clinical association between migraine and sleep-disordered breathing. In addition, sleep of children with severe migraine was characterized by a shorter duration of sleep time and higher sleep latency compared to children with milder migraine, while chronic migraine was associated with more disrupted sleep (ie, a higher arousal index than in children with migraine).

**Potential mechanisms underlying migraine and sleep disorders**

Sleep represents the only well-documented behavioral state related to the occurrence of some headache syndromes, and this correlation is linked to common pathophysiologic substrates, especially hypothalamus, serotonin, and melatonin.\textsuperscript{11}

The structure recognized to be a migraine generator is the trigeminal nucleus caudalis in the pons and midbrain, but the hypothalamus is also surely involved in the prodromal symptoms of migraine, such as yawning, hunger, cravings, fatigue, mood changes, and sensory and visual distortions, that are commonly considered as dopaminergic premonitory symptoms.\textsuperscript{6,7,77} The hypothalamus is connected with the limbic system, the pineal gland, the noradrenergic locus coeruleus, and the serotonergic dorsal raphe, which are anatomical structures involved in the control of the sleep–wake cycle as well as in the modulation of pain.\textsuperscript{78} The serotonergic system, in particular, might play an important role in the relationship between headache and sleep.

Also, dopamine is important in the pathogenesis of migraine: individuals susceptible to migraine appear to have genetic polymorphisms in the dopamine D\textsubscript{2} gene, which increase responsiveness to dopamine, or defects in tyrosine hydroxylase, which inhibits dopamine metabolism, and an imbalance of the dopaminergic system is responsible for some premonitory symptoms of migraine, such as nausea, yawning, and dizziness.\textsuperscript{79,80} Finally, melatonin is a chronobiotic substance that has demonstrated therapeutic efficacy in some forms of migraine and headache.\textsuperscript{42,81,82}

Based on this body of evidence, different studies have proposed a model of interaction between headache and sleep\textsuperscript{77,74,83} by combining clinical data and experimental evidence. The interrelationship between sleep and headache can be summarized as follows:\textsuperscript{11}

- (a) sleep could be a trigger factor for headache (excessive, reduced or disrupted, increased deep sleep can all determine the onset of the pain attack);
- (b) sleep is often used by patient as relieving factor for headache;
- (c) sleep disturbances can cause headache (ie morning headache in sleep apnea patients);
- (d) bad sleep hygiene can worsen a pre-existing headache;
- (e) sleep disorders are often present in headache patients (ie parasomnias, sleepwalking);
- (f) headache attacks occurring during the night can be cause of sleep disturbance;
- (g) headache can be related to specific sleep stages (REM or SWS);
- (h) headache occur mostly during sleep or just after sleep;
- (i) the association between headache and sleep is mediated by the same neurotransmitters (serotonin/dopamine).

The hypothesized structural alteration of serotoninergic and dopaminergic pathways affecting migraine and sleep might be at play from the early period of life, leading to disorders of the sleep–wake rhythm in infancy that tend to persist during childhood and adolescence, and to the development of a comorbid headache disorder as result of this neurotransmitter imbalance.\textsuperscript{70,84,85}

From the anatomical point of view, the intrinsic mechanism that leads to headache relief is still unknown and understudied. It is known that the processing of pain interacts with other vegetative functions, such as sleep, arousal, and sympathetic, parasympathetic, and neuroendocrinological functions.

As already reported, the hypothalamus has a crucial role in both headache and sleep disorders, and is strictly correlated with brain areas involved in the pathogenesis of migraine. The hypothalamus is closely connected with the limbic system, the retinohypothalamic tract, and brain-stem aminergic nuclei (including those of the dorsal raphe and the locus coeruleus). This anatomical framework can explain the autonomic symptoms that are the specific presentation of the migraine syndrome. Furthermore, the hypothalamus is connected with the antinociceptive system represented by the rostroventromedial medulla oblongata, the serotonergic raphe nuclei, the noradrenergic locus coeruleus, and the periaqueductal gray (PAG) matter. The ventrolateral part of the PAG is probably the most interesting anatomical region for the connectivity of headache and sleep: it can
cause “rapid-eye-movement sleep-off” when activated by orexin. Furthermore, orexin can stimulate neurons in the ventrolateral part of the PAG, which inhibits antinociceptive activity in the trigeminal nucleus caudalis (ie, facilitates trigeminal nociception), triggering a migraine attack. The orexinergic neurons of the posterior hypothalamus are involved both in inhibition of analgesia and in sleep disorders such as narcolepsy. Dysfunctional hypothalamic activity might contribute to both altered sleep–wake function and altered pain processing via its orexinergic neurons.

It is therefore very likely that pain processing can be modulated via these circuits by vegetative/autonomic symptoms and reflex mechanisms: sleep can trigger a migraine attack (involving the posterior hypothalamus and orexinergic system), and on the other hand, through changes of the autonomic homeostasis, it can facilitate or suppress pain processing.

**Conclusion**

Clinical, anatomical, biochemical, and pathophysiologic evidence supports the association between sleep and the genesis of headache in biologically predisposed persons.

Summing up the review, we can conclude that the prevalence studies demonstrated a relationship between headache and sleep disorders based mainly on association and not on causality. Polysomnographic studies indicated a strong clinical association between migraine and sleep-disordered breathing.

On the other hand, lack of sleep or excessive sleep duration can represent a causative factor for headache, and circadian abnormalities seem to have a triggering role for headache attacks, suggesting a causality or reinforcement in subjects with headache.

This relationship is most evident for primary headache disorders and especially in childhood; in this view, sleep problems are considered as predisposing, predictive, or even prognostic factors for headache development or endurance. In children and adolescents with a predisposition to headache, any disruption of sleep or a simple alteration of the sleep–wake cycle might lead to the onset of an acute headache attack.

The hypothesized structural alteration of the neurotransmitter (serotonergic and dopaminergic) pathways affecting migraine and sleep might be active from the early period of life, leading to disorders of the sleep–wake rhythm in infancy that tend to persist during childhood and adolescence and to the development of a comorbid headache disorder.

Therefore, the clinical evaluation of childhood headache should include a careful analysis of sleep habits and patterns and the evaluation of the presence of sleep disturbances, in order to develop better treatment methods for both sleep and headache.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


