Chapter 13
Comorbidity with Sleep Disorders

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13.1 Introduction

The reciprocal relationship between headache and sleep has been documented in medical literature for over a century, and clinical texts allude to the importance of sleep as a headache precipitant. The precise nature and magnitude of the headache/sleep association and underlying mechanisms remains poorly understood [1].

Both sleep disturbances and headache disorders are widespread health problems during childhood: migraine and tension headaches alone occur in approximately 12% of the pediatric population, and 25% of children have experienced at least one type of sleep problem [2, 3].

Sleep represents a well-documented behavioral state related to the occurrence of some headache syndromes. Sleep disorders are observed among all headache subgroups, and headaches that occur during or after sleep are suggestive of sleep disorders.

In the adults, the presence of a specific sleep disorder has been identified in 55% of subjects with onset of headache during the night [4], and the treatment of the

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underlying sleep disorders improved the headache. More recently [5] a direct correlation between the increase in sleep disturbance and headache severity has been found.

Sleep disorders are the most frequent comorbid disorders in children with migraine, followed by anxiety disorders and depression; further, 66% of migraine children with sleep disorders had enduring headache [6]. In young children not able to report correctly the symptoms, owing to immature language and cognitive abilities, migraine descriptors can be missed, or sleep disturbances may not be recognized as causative factors for migraine [7]. For these reasons some manifestations related to sleep can be missed or misdiagnosed. Similarly, childhood periodic syndromes that are difficult to diagnose are thought to represent early-life expression of migraine genes that later in life are expressed as migraine headache and include benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclic vomiting syndrome. Recent research suggests infant colic may also fit into this category [8].

On the other hand, headache may cause various degrees of sleep disruption and seems to be associated with several sleep disturbances either in adults or in children.

From the headache perspective, a sleep disturbance (too much, too little, inappropriate timing, or inappropriate sleep behavior) can be a trigger for headache, but sleep commonly also terminated the attack; on the contrary, headache might be a symptom of sleep disturbance and side effect of sleep- or wake-modulating treatments [9, 10]. Furthermore, both conditions highly increase the risk for each other.

The mutual interactions between sleep and headache are mediated by:

(a) Time of occurrence (headache occurs during sleep, after sleep, and in relationship with sleep stages).
(b) Quantitative associations (excess, lack, bad quality, or short duration of sleep may trigger headache).
(c) Reciprocal link with pain: noxious stimuli and painful disorders interfere with sleep, and sleep disturbances affect pain perception.

Sleep deprivation and sleep schedule changes are common headache triggers for both migraine and tension-type headache, and even in children, one of the commonest self-perceived triggers of head pain was the lack of sleep [11], and on the other hand, sleep seems efficacious to relieve head pain or terminate the headache attack [12, 13]. Frequency of falling asleep during attacks is significantly more common in patients <8 years of age than in older children, and in these children, there is higher resolution of attacks with sleep [14].

An hypothesis on the intrinsic mechanism for which sleep determined the head pain relief is that sleep could trigger an autonomic reset [15].

Another important point in favor of this strict relationship comes from the fact that treating headache improves sleep (5-HT, serotoninergic drugs), and, conversely, that treating sleep improves headache (CPAP treatment, sleep hygiene, dopaminergic agents for restless legs syndrome, stimulant for narcolepsy, fibromyalgia treatment) [16].

13.2 The Specific Links Between Headache and Sleep in Infants and Children

Several studies in headache children reported that the major sleep complaints are linked to reduced sleep duration, bedtime settling, longer sleep latency, night awakenings, and nocturnal symptoms like nightmares, parasomnias, or restless sleep and daytime sleepiness [17–19].

Subjects with migraine reported a higher prevalence of sleep disturbances in parents, sleep disturbances in infancy, and colic, as well as an elevated level of familiarity for migraine, 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 [20].

Furthermore, sleep problems during infancy can be a predictive factor for the development or persistence of headache. Sleep disorders in the first months of life were found to be present in 78% of children with enduring headache vs. 25% of children showing headache remission [21].

The strict correlation between sleep and headache has been also supported by a research showing that sleep disruption at age 3 predicted headaches at 6 years [22].

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 [20]. Frequency and duration of migraine attacks predicted specific sleep disturbances such as sleep anxiety, parasomnias, and bedtime resistance [23].

In further support of this association, it has been demonstrated that the lack of sleep (69.6%) was the second disorder most commonly reported by children, preceded only by stress (75.5% of patients), followed by climate changes (68.6%), and video games (64.7%). Accordingly, in a large epidemiologic study on childhood migraine, our group reported that "a bad sleep" was found to be the primary predisposing or causative factor for headache attacks followed by emotional distress [24].

An early precursor of migraine could be represented by infantile colic, which represents one of the earliest manifestations of pain and crying in healthy infants. This association has been corroborated by sporadic reports showing an increased prevalence of infantile colic in migraine children and by a longitudinal study of hyperreactive infants, that is, infants exhibiting irritability, infantile colic, and crying bouts during their first months of life [25, 26].

A positive history of colic was reported in 38.4% of subjects with migraine, significantly higher than in controls (26.9%) and in subjects with TTH (25.2%) [20].

This was confirmed by another study showing an increased positive history of colic in children with migraine (52% vs. 20% in controls) [25]. In another recent study, 208 consecutive children with migraine aged 6–18 years presenting to the emergency department were more likely to have experienced infantile colic than those without migraine (72.6% vs. 26.5%; $p < 0.001$), either migraine without aura (73.9% vs. 26.5%; $p < 0.001$) or migraine with aura (69.7% vs. 26.5%; $p < 0.001$).

This association was not found for children with tension-type headache (TTH) (35% vs. 26.5%), confirming the specificity of the association [27]. This association was not found for children with TTH (35% vs. 26.5%), confirming the specificity of the association. In one report, an infant with colic experienced improvement after starting antimigraine (cyproheptadine) therapy, reinforcing the relationships between the two conditions [26].

13.3 Sleep Disorders and Headache in Infants and Children

Literature data showed that the most common sleep disturbances found in children with headache are represented by insufficient sleep, difficulties falling asleep, anxiety related to sleep, restless sleep, night waking, nightmares, daytime sleepiness, and parasomnias [28].

One of the first study on a large group of pediatric patients with headache showed that both migraine and tension headache were associated with different sleep disorders, but the migraine group tended to have "a more disturbed sleep" with increased prevalence of nocturnal symptoms, such as sleep breathing disorders, restless sleep, and parasomnias and of daytime sleepiness [20]. This questionnaire-based study involved 283 headache sufferers 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 TTH and 35 chronic TTH), compared with an age-matched healthy control (C) group. Significant differences between headache and controls were found: children with migraine and TTH presented shorter sleep duration and longer sleep latency, a higher prevalence of difficulty falling asleep, and sleep disruption, with more than two awakenings per night. Some parasomnias were more prevalent like sleep talking, bruxism, and reports of frightening dreams, whereas no differences were observed for sleepwalking, bed-wetting, or sleep terrors. Sleep breathing problems were more frequent in subjects with migraine, while restless sleep and daytime sleepiness occurred more frequently in subjects with migraine and tension headache vs. controls.

No significant differences were found between the migraine and headache groups.

Other researchers confirmed that children with migraine have a large range 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 [7, 29, 30].

An old report in 48 children with headache confirmed the association of primary headache with night wakings (41.7%), difficulty falling asleep (20.8%), pavor nocturnus and nightmares (14.6%), enuresis (8.3%), and somnambulism (6.3%) [31].

Another study reported a high rate of sleep disturbances in children, sleeping too little (42%), bruxism (29%), cosleeping with parents (25%), and snoring (23%) and also showed that the frequency of migraine predicted parasomnias, whereas duration of migraine predicted sleep anxiety and bedtime resistance [23].

A more recent report confirmed the presence of excessive daytime sleepiness, narcolepsy, and insomnia in children with headaches while failed to corroborate the higher prevalence of symptoms of sleep apnea, restlessness, and parasomnias, reported in the previous studies [32].

A study showed that migraine without aura was a sensitive risk factor for disorders of initiating and maintaining sleep and chronic tension-type headache for sleep breathing disorders and that headache disorder as a whole was a cumulative risk factor for disorders of excessive somnolence [33].

13.3.1 Non-Rapid Eye Movement Sleep Parasomnias

Several reports have described the association between headache and parasomnias in children. The first studies showed a correlation between sleepwalking and migraine: Barabas et al. [34] in four groups of patients (60 with migraine, 42 with non-migraine headache, 60 with epilepsy, and 60 with learning disabilities/neurologic impairment) found history of at least two episodes of somnambulism in 30% of migraineurs vs. 4.8% of those with non-migraine headaches, 5% of those with learning disabilities/neurologic impairment, and 6.6% of epileptics. Pradalier et al. [35] found an incidence of sleepwalking in 21.9% of migraine subjects vs. 6.6% of controls. Giroud et al. [36] found history of somnambulism in 29.4% of migraine subjects vs. 5.4% of non-migraine headache subjects.

However, the association between migraine and parasomnias is not limited to sleepwalking but includes also pavor nocturnus and enuresis: Dexter [37] found an incidence of 71% of pavor nocturnus (vs. 11% of controls), of 55% of somnambulism (vs. 16% of controls), and of 41% of enuresis (vs. 16% of controls).

These findings are in agreement with some studies [20, 23], while another research failed to confirm this increased prevalence of parasomnias [32].

A recent study evaluated the predictive value of sleep terror history in childhood for the development of migraine in adolescence, based on the higher prevalence of a history of sleep terrors (40%) in adolescents with chronic migraine vs. those with episodic migraine (26%) and healthy controls (8%) [38].

It has been hypothesized that somnambulism and migraine can appear at different ages, the former in the late infancy, the latter in childhood, representing a different age-related expression of a disorder of serotonin metabolism. Furthermore, there is some evidence that sleepwalking and headache can be precipitated by sleep-disordered breathing [39].

The hypercapnic acidosis, secondary to sleep-disordered breathing, could stimulate the serotonergic neurons, resulting in increased excitability of motoneurons leading to the appearance of somnambulism. Further, the need for concomitant age-related increased excitability of 5-hydroxytryptamine (5-HT) neurons and acidosis explains why abnormal breathing during sleep only rarely induces sleepwalking in adults [40].

13.3.2 Sleep-Disordered Breathing

Few data are available on the relationship between sleep apnea and headache or 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 [41]. A varied range of symptoms and signs are associated with OSAS in 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 [42].

In adults the prevalence of headache in (OSAS) patients is very high: Neau et al. [42] showed that 33% of OSAS patients had headaches, of whom 58.5% had morning headaches. However, it seems that early-morning headache is a not specific symptom of sleep apnea [43]; in fact, patients with abnormal sleep complained of early-morning headache even more frequently than patients with OSAS confirming the hypothesis that migraine attacks could be secondary to sleep disruption rather than to sleep apnea.

Hypercarbia, hypoxemia, altered cerebral blood flow, increased intracranial pressure, alterations in sympathetic nerve activity, rises in blood pressure secondary to multiple arousals, and brainstem dysfunction have been reported as etiologic or worsening factors for headache in patients with OSAS [42]. However, it has been hypothesized that migraine attacks could be secondary to sleep disruption rather than to sleep apnea by itself.

A polysomnographic study in children with headache indicated that sleep-disordered breathing was more frequent among children with migraine (56.6%) and nonspecific headache (54%) vs. chronic migraine (27%). These findings revealed a strong clinical association between migraine and sleep-disordered breathing, whereas chronic migraine was associated with more disrupted sleep and tension-type headache with bruxism [44].

Future studies may characterize the headache in OSAS patients to address the question if sleep apnea is the primary event leading to headache or if sleep disruption is the main pathogenetic factor for morning headache.

13.3.3 Restless Legs Syndrome

Restless legs syndrome (RLS) is characterized by an urge to move the legs, accompanied by unpleasant leg sensations, occurring at night, worsened by rest, and improved by movements. There is accumulating evidence that RLS is another condition that is frequently reported by patients with migraine, adults or children. RLS prevalence in migraine has been reported to range from 8.7 to 39.0%, with no apparent differences in gender and aura status, whereas migraine prevalence in RLS ranges from 15.1 to 62.6% [45].

Chen et al. [46] found that RLS was more common in migraine patients (11.4%) than in TTH (4.6%) and chronic headache (2.0%). Another study confirmed the higher occurrence of RLS in migraine adults but also suggested that RLS (the condition itself or the disruption of sleep patterns often found in patients affected by RLS) might affect migraine clinical presentation, being associated with chronic and highly disabling migraine [47].

A common pathophysiological origin for migraine and RLS has been proposed [48] with a link involving a disturbance of iron and a dysfunction within the dopaminergic system. This notion is supported by the rapid improvement of RLS symptoms after treatment with dopaminergic agents [49].

Dopamine is involved in migraine pathophysiology. In particular, dopaminergic premonitory symptoms like yawning, irritability, and mood changes, as well as nausea and vomiting, occurring during both the premonitory and headache phases, may be caused by dopamine and are present in 47.6% of patients with RLS and migraine but only in 13.1% in those without RLS [50].

Moreover, the risk of having RLS is increased in patients with migraine [45] and is 45 times higher in the presence of dopaminergic premonitory symptoms [51].

Only 1 pediatric study on children and adolescents aged 5–18 years focused on the correlation between RLS and headaches: 24 patients with migraine (21.6%), 4 (5%) headache-free controls, and 9 (8.3%) healthy children met the diagnostic criteria for definite RLS. This study showed an approximately fourfold higher frequency of RLS in pediatric patients with migraine compared with headache-free controls [52].

Based on the dopaminergic hypothesis, another recent study investigated daytime dysfunction in 25 children with RLS and the effects of treatment primarily with iron supplements on RLS symptoms. Following treatment, participants' daytime function had improved to levels similar to those of controls. Sixteen out of twenty-three cases were successfully treated primarily with iron supplement [53].

13.3.4 Periodic Limb Movements (PLMS)

There is only one published study on the prevalence of PLMS and migraine and their relationship with disability and pain intensity in a pediatric group of patients. Polysomnographic evaluation showed periodic limb movement index (PLMI) 45/h in 26.47% of children with migraine; these subjects with PLMI 45/h presented higher frequency, intensity, duration, and life impairment of migraine and lower efficacy of prophylactic and acute pharmacologic treatment, with respect to children with migraine without aura and normal PLMI. 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 [54].

13.3.5 Sleep Bruxism (SB)

SB, a sleep-related movement disorder characterized by teeth grinding and clenching, is frequently associated with orofacial pain and headaches. Children with SB may report approximately three times as many headaches than non-SB subjects with an odds ratio of 4.3; on the other hand, children with migraine showed a high prevalence (29%) of SB [55].

13.3.6 Narcolepsy

Patients with narcolepsy often reported suffering from headache independently from the drug administration.

Patients with narcolepsy fulfilled the criteria for tension headache significantly more often than by controls (60.3% vs. 40.7%) [56], and migraine prevalence showed a twofold to fourfold increase in patients with narcolepsy. The onset of narcolepsy symptoms is preceded by 12.3 years the onset of migraine symptoms. The increased prevalence of migraine was independent of the pharmacologic treatment of narcolepsy and of severity of narcolepsy symptoms [57].

No studies are available on the prevalence of migraine in children and adolescents with narcolepsy, and headache has often been reported as a side effect of treatment in these children [58].

The relationship between narcolepsy and migraine might be mediated by the orexinergic neurons of the posterior hypothalamus that are involved both in inhibition of analgesia and in narcolepsy [59].

13.4 Treatment for Migraine and Sleep in Children

Taking into account the connection between sleep and migraine could guide the correct treatment of migraine [15].

Sleep deprivation may enhance the response to pain stimuli and can trigger the migraine attacks [60, 61], but it seems that sleep continuity disturbance, rather than simple sleep restriction, impairs endogenous pain-inhibitory function and increases spontaneous pain [62].

Some drugs could improve migraine by reducing the sleep deprivation and improving the sleep continuity with a secondary effect on the pain threshold.

13.4.1 Non-pharmacologic Treatment

The use of non-pharmacologic preventive measures in children with migraine includes lifestyle adjustments (dietary changes, sleep hygiene), reassurance, stress management, biofeedback, relaxation techniques, and other behavioral therapies [63–65].

A recent study applied a non-pharmacologic treatment for migraine in 32 preschool children, and 60 older school-age children instructed to follow (a) sleep hygiene, (b) proper diet (refraining from food additives, with elimination of smoked lunch meats, smoked cheese, yellow cheese, chocolate and foods containing chocolate, pizza, and foods containing monosodium glutamate), and (c) no direct sun exposure. Mean age of the patients with no response to treatment was 10.6 ± 3.2 years, partial response 9.11 ± 4.6 years, and complete response 8.11 ± 3.9 years. The percentage of patients with complete to partial response was significantly higher in the younger group demonstrating that children younger than 6 years were more sensitive than older children to non-pharmacologic treatment [64].

In a pioneering study, the sleep hygiene rules have been applied to 70 children and adolescents with migraine. Patients showed a reduction in the mean duration and frequency of migraine attacks, while the severity of the attacks did not change.

In this study, based on the presence of at least two criteria for defining poor sleep hygiene, 70 migraineurs (42.7%) have been selected in a group of 164 migraine patients and randomly assigned to group A or B. The A group had been instructed to follow instructions to improve sleep hygiene; the B group did not have instructions on improvement of sleep hygiene.

After 6 months of follow-up, the sleep hygiene group reported lower mean headache duration than the control group, suggesting that better sleep quality led to altered migraine patterns. The frequency of migraine attacks showed also an improvement: at the first observation, the prevalence of A group subjects with more than one attack per week was 35%; at 3 months the number decreased to 15% and at 6 months it was 11%. In the B group, the percentage did not change significantly (at first observation, 42%; at 3 months, 37%; and at 6 months, 33%). Severity of migraine attacks was not affected by the sleep hygiene treatment [24].

Although this study represents an indirect measure of the effects that sleep disturbances can have on migraine, it supports the direction of the relationship (i.e., sleep disturbance can exacerbate migraine).

It has been reported that sleep has the power to stop the pain phase of headache attacks. Preschool-age children, especially under 6 years of age, have longer sleep duration, and they often sleep more easily during the day [66].

It is therefore possible that their shorter attacks depend on easier initiation of active mechanisms such as sleep stopping the pain phase.

13.4.1.1 Treatment of Sleep-Disordered Breathing to Improve Migraine

No data are available on the treatment of sleep apnea and migraine in children, but there are some studies showing that morning headache was totally resolved in 90% of patients treated with nasal CPAP [67].

A recent study provides new insights into the effectiveness of the mandibular advancement appliance (MAA) for treating headache associated with sleep bruxism. Sixteen adolescents reporting SB, headache, or snoring underwent four ambulatory PSGs for baseline and while wearing MAA during sleep for 1 week. Sleep bruxism index decreased up to 60%, and headache intensity showed a decreasing

trend with MAA [68]. However, interactions between sleep bruxism, breathing during sleep, and headache as well as the long-term effectiveness and safety of the MAA in adolescents need further investigation [55].

13.4.2 Pharmacotherapy

Based on the similarities in pathophysiology, it is not surprising that the drugs used for prophylaxis or treatment of migraine can improve sleep and vice versa.

In contrast to the large number of adult trials, relatively few trials have evaluated prophylactic treatment of pediatric headaches [69]. Different drugs have been used for headache/migraine prophylaxis like topiramate, trazodone, clonidine, flunarizine, pizotifen, propranolol, and valproate. Apart from these drugs, there are some compounds that act either on pain threshold or by modifying/improving sleep. These drugs, commonly used also in children, are mostly represented by antihistaminics, melatonin, and serotoninergic drugs.

13.4.2.1 Antihistaminics

Alterations in the histaminergic system have been proposed both in neurological and psychiatric diseases hypothesizing also a role as a potent modulator of meningeal nociceptors' activity in migraine. Activation of inhibitory H3 receptors has been suggested for migraine prophylaxis, and both H3R and H4R ligands may theoretically have prophylactic properties. Despite being promising drug targets for several diseases, the lack of specificity and undesired side effects discouraged the potential exploratory studies [70].

Cyproheptadine, an antagonist at the 5-HT2, histamine H1, and muscarinic cholinergic receptors, is widely used in the prophylactic treatment of migraine in children. The total dose ranges from 12 to 36 mg per day (given two to three times per day or at bedtime). Common adverse events are sedation and weight gain; dry mouth, nausea, lightheadedness, ankle edema, aching legs, and diarrhea are less common. Cyproheptadine may inhibit growth in children and reverse the effects of SSRIs. A single class II study showed cyproheptadine (4 mg per day) was as effective as propranolol (80 mg per day) in reducing migraine frequency and severity [71].

We can assume, however, that the antihistaminics could act in migraine indirectly through the improvement of sleep, and this effect could decrease the pain in migraine children.

13.4.2.2 Melatonin

There is evidence that melatonin, besides having a role in the biological regulation of circadian rhythms, sleep, mood, and aging, is also involved in various headache syndromes, including migraine and tension headache.

Melatonin may play a role in headache pathophysiology via several mechanisms. The antinociceptive effects of melatonin have been demonstrated in animal models, both in inflammatory and neuropathic pain [72, 73].

Beside the other several actions on different receptors, melatonin also reduces the upregulation of a variety of pro-inflammatory cytokines, interleukins, and TNF-alfa and affects the activity of nitric oxide synthase. It also decreases dopamine and glutamate release and potentiates the receptor-mediated response of GABA and the opioid immune response and modulate serotonin release [74, 75].

All these evidences supported the use of melatonin in patients with headache or migraine, and circadian rhythm disorders related also to the demonstration of a decrease of melatonin levels in these individuals [76, 77]. Furthermore, a decreased nocturnal melatonin secretion has been reported in patients with both migraine [78] and cluster headache [10]. The efficacy of melatonin in these cases could be related to regularization of the sleep-wake pattern through its chronobiological and "sleep hygiene" effect [79].

Despite several studies demonstrating a decrease of melatonin levels in adults with migraine, a recent report showed no significant difference in urinary 6-sulfatoxymelatonin between the migraine children and control group, indicating that nocturnal production of melatonin is not reduced in children with migraine [80].

A recent research showed that melatonin treatment decreased headache in 78.6% of 328 patients with circadian rhythm sleep disorders and headache while induced (slight) headache in 13.8% of 676 patients with circadian rhythm sleep disorders without headache [81].

In an open-label trial in children with primary headache, melatonin 3 mg twice daily reduced the number (by more than 50%), intensity, and duration of headache attacks in 14 of 21 children, showing a better efficacy in migraine vs. tension headache form [82].

A study of melatonin in a single dose of 0.3 mg/kg for 3 months indicated that melatonin might be considered as an effective and safe drug in the prophylaxis of migraine in children. Monthly frequency of attacks reduced from 15.63 ± 7.64 to 7.07 ± 4.42, severity scores from 6.20 ± 1.67 to 3.55 ± 2.11, and duration of headache, from 2.26 ± 1.34 to 1.11 ± 0.55 h. Pediatric Migraine Disability Assessment score decreased from 31.72 ± 8.82 to 17.78 ± 10.64 [83].

However, all these studies were nonrandomized and conducted in small samples; therefore there is still no definitive consensus about the therapeutic use of melatonin for headache in children.

13.4.2.3 Serotonergic Drugs

A congenital alteration of neurotransmitter pathways (serotonergic and dopaminergic) might predispose individuals to sleep disorders and to headache, a result of this neurotransmitter imbalance [84] that might act since the early period of life determining sleep disorders during infancy (i.e., colic, insomnia) followed by the development of migraine later in life [14].

Serotonin (5-HT) decrease may lower the threshold of pain perception but also might act through a derangement of sleep structure and predispose to headache [85], but 5-HT also plays significant roles in modulation of sleep [86]. It has been further demonstrated that a reduction in brain synthesis of 5 HT intensifies photophobia and other migrainous symptoms [87].

A recent study investigated the plasma tryptophan, 5-hydroxytryptophan (5-HTP), 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) levels in migraine adults patients with (MWA) or without aura (MWoA) and in controls. The plasma 5-HT level was significantly lower in MWA patients than in the controls, whereas no significant difference was observed between the levels in MWoA patients and controls. On the other hand, the plasma 5-HTP and 5-HIAA levels were not significantly different between the MWA patients, the MWoA patients, and the controls. These data suggest that an enzymatic dysfunction in the metabolic pathway from 5-HTP to 5-HT may be present in MWA patients [88].

A double-blind crossover study of 27 migraine children aged 6–12 years treated with L-5HTP (5 mg/kg body weight) vs. placebo showed that both L-5HTP and placebo led to a significant reduction of the migraine index and frequency of migraine attacks with no differences on final efficacy [89].

On the other hand, another report on 48 elementary and junior high school students with primary headache associated with sleep disorders showed that treatment with L-5-HTP in these patients determined the improvement of both conditions, headache and sleep disorders, in particular frequent awakenings and some parasomnias [31].

Tricyclic antidepressants are used for migraine prevention; however, only one tricyclic antidepressant (amitriptyline) has proven efficacy in migraine.

The mechanism by which antidepressants work to prevent migraine headache is uncertain, but they are useful in treating many chronic pain states, including headache, independent of the presence of depression, and the response occurs sooner and at lower dosages than that expected for an antidepressant effect. The antidepressants that are clinically effective in headache prevention either inhibit norepinephrine and 5-hydroxytryptamine (5-HT) reuptake or are antagonists at the 5-hydroxytryptamine 2 (5-HT2) receptors.

A randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg per kg of body weight per day), topiramate (2 mg per kg per day), and placebo in children and adolescents 8–17 years of age with migraine showed no significant between-group differences in the primary outcome (50% reduction of attacks), which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group. There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Amitriptyline adverse events were fatigue (30%) and dry mouth (25%), and three patients had serious adverse events of altered mood [90].

13.5 Conclusion

A better understanding of the pathophysiology and the high comorbidity between the migraine or headache and disturbed sleep could be helpful both in diagnoses and management of the headache syndromes.

In the last few years, several studies have converged in demonstrating that the link between sleep and migraine is more complex and not limited to the association with parasomnias or sleep apnea but also with RLS, PLMS, and narcolepsy. Sleep disturbances, therefore, are now viewed as comorbid, predisposing, predictive, or even prognostic factors for headache development or endurance.

Almost all of the pharmacological studies in children with migraine have not included the evaluation of any sleep parameters, but we believe that screening for sleep disorders with the use of proper tests including PSG and referral to a sleep clinic when appropriate could be very helpful. Patient education and lifestyle modification including sleep hygiene might play a significant role in overall success of the treatment. It is important for the clinicians to perform the clinical evaluation of childhood 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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