Review Article

Primary Headaches and Sleep Disorders: Review of Literature about Comorbidity in Children and Adolescents

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Abstract

Sleep disorders and primary headaches are frequent health problems in childhood, and they are often comorbid in an individual, linked by a mutual and complex relationship. This comorbidity is frequent and well documented, but the available literature is usually biased in favor of one aspect or another, mainly depending on the expertise of the authors. The aim of this article is to review existing literature on the comorbidity between primary headaches and sleep disorders in pediatric age and summarize the heterogeneous results. Our findings, involving a total of 12 studies and 16.474 subjects aged 2–18 years, indicate a bidirectional and strong relationship between headache and sleep disorders in childhood, with multiple associations between headache features and sleep disturbances. This can be explained by many common pathophysiologic pathways. Improving sleep quality could help to reduce migraine intensity and disability and vice versa.

Keywords: *Childhood, children, comorbid conditions, comorbidity, migraine, pediatrics, pathophysiology, primary headaches, sleep disorders, tension-type headache*

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Introduction

Headaches and sleep disorders are frequent health problems in children. Primary headaches, among which migraine is the most common form,[1] occur in 12% of the pediatric population, and the prevalence increases throughout childhood and adolescence.[1,2] Sleep disorders occur in 24% of children.[2]

Furthermore, headaches might be a consequence of a disrupted sleep, which in turn might increase the severity of attacks and promote chronicization.[3]

Growing neuroscientific evidence considers migraine and sleep disorders as manifestations of common underlying pathophysiological mechanisms, sharing common cerebral structures such as the hypothalamus and raphe nuclei, common mediating signaling pathways including serotoninergic system, and the recently described glymphatic system.[4]

Moreover, there are common risk factors, such as mood and anxiety comorbidity disorders, associated with both headache and sleep disorders.[5]

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To partially fill this gap of knowledge, the aim of this paper is to review existing literature on the comorbidity between primary headaches and sleep disorders in pediatric age and summarize the heterogeneous results.

Materials and Methods

The review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure and adheres to a structured review protocol.[6] To establish the research question, the PICO-model PICOS (Patient, Intervention, Comparison, and Outcome) according to the PRISMA guidelines was used:[7]

- Patient: Children with sleep disorders and primary headache

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- Intervention: Review existing literature on the diagnostic assessment of primary headache in comorbidity with sleep disorders
- Comparison (not available)
- Outcome: Investigate the presence of comorbidity between primary headaches and sleep disorders.

Search strategy and article selection

Two authors, during June and July 2023, performed a comprehensive search of the databases PubMed using the following keywords in the title and in the abstract:

- "Primary headache" OR, AND "sleep"
- "Primary headache" OR, AND "sleep disorders"
- "Primary headache" OR, AND "sleep disturbance"
- "Migraine" OR, AND "sleep"
- "Migraine" OR, AND "sleep disorders"
- "Migraine" OR, AND "sleep disturbance."

Figure 1 shows the flowchart of the search strategy for articles selection. In the first stage, the studies were selected according to the following occurrences:

- Involved individuals with headaches and sleep disorders
- Involved children and adolescents up to 18 years of age
- Reported the diagnostic evaluation methods for headaches and sleep disorders
- English language
- Published within 20 years from the research date.

Differently, the studies were excluded according to the following occurrences:

- Review articles, case reports, letters, meta-analyses, and books
- Treatment studies (both pharmacological and nonpharmacological)
- Studies in which subjects presented other neurological disorders, such as epilepsy, or wherein the presence of headaches was addressed chiefly as a symptom in the context of other general medical conditions, or that dealt with neurodevelopmental disorders such as children with intellectual disability, borderline intellectual disability, psychiatric disorders, attention deficit hyperactivity disorder, and tics
- Sleep disorders secondary to nocturnal enuresis
- Studies that relied exclusively on neurophysiological methods, since these are recognized and valid methods to study sleep characteristics but represent second-step investigations, as they are not used in the daily clinical practices.

In the second stage, two authors – independently – screened all the titles and abstracts of the studies identified by the first-stage search, reading the full text according to the inclusion criteria previously defined. The full text of an article was recorded in the review when both reviewers agreed that it might fulfill the inclusion criteria. Articles were reviewed for relevance and excluded if they did not include data relating to the diagnostic methods applied to evaluate the presence of sleep disorders and/or headaches.

Results

After the initial identification of 36 papers, we selected 12 papers [Table 1] that fulfilled our inclusion criteria.

The reported results from all of these studies involved 16.474 subjects aged 2–18 years. Eleven out of 12 studies diagnosed headaches according to the ICHD criteria, and a single one used country-specific diagnostic criteria, which are not specified Table 1.[7,12,18] Primary headaches detected were migraine with and without aura, chronic migraine, tension-type headache, new daily persistent headache, and probable migraine. Several authors used specific tools to evaluate the severity of headaches, such as Pediatric Migraine Disability Assessment Score, Numerical Rating Scale, Wong–Baker Faces Pain Rating Scale, Headache Intake Questionnaire, and other self-made tools.[3,6-8,10,11]

Different types of sleep disorders emerged: insomnia, disturbances of the sleep–wake rhythm (insufficient total sleep, difficulty falling asleep, bedtime resistance, and night wakings), obstructive sleep apnea syndrome, daytime sleepiness, parasomnia, hypersomnia, sleep anxiety, snoring, and other unspecified sleep disorders. Different studies used validated questionnaires, including the Children's Sleep Habits Questionnaire, Sleep Disturbances Scale for Children, Pediatric Daytime Sleepiness Scale, Epworth Sleepiness Scale for Children

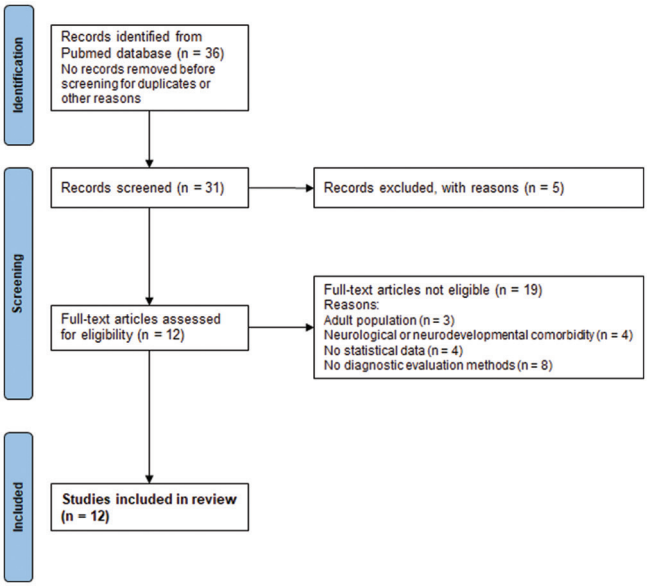

Figure 1: Inclusion process flowchart

Table 1: Main characteristic of selected studies

Reference	*n*	Age (years)	Headache type	Headache diagnosis	SD type	SD diagnosis	Main pathology analyzed
1. Gilman *et al*., 2007[8]	69	13–17	MwA, MwoA, TTH	ICHD-2	DTS, NW, insufficient total sleep, difficulty falling asleep	CSHQ	Headache + SD
2. Esposito *et al*., 2013[9]	271	6–13	MwoA	ICHD-2	DTS, SDB, disorders in initiating and maintaining sleep, disorders of arousal, sleep–wake transition disorders, nocturnal hyperhidrosis	SCDS, PDSS	Headache + SD
3. Heyer *et al*., 2014[3]	52	10–18	Migraine, PM	ICHD-2	Sleep disturbances directly related to proximate headaches	None	Headache + SD
4. Rabner *et al*., 2018[5]	527	7–17	Migraine, TTH, NDPH	ICHD-2	Sleep disturbance, unspecified	SHIP	Headache + SD
5. Rabner *et al*., 2017[10]	1078	7–17	Migraine, TTH, NDPH, mixed headache presentation	ICHD-2	Sleep disturbance, unspecified	SHIP	Headache + SD
6. Heng and Wirrell, 2006[11]	51	6–18	MwA, MwoA	ICHD (unspecified)	BTR, SOD, SLD, SA, PS, SDB, DTS, NW	CSHQ	Headache + SD
7. Cheraghi *et al*., 2018[12]	198	6–12	Migraine, TTH	Country-specific diagnostic criteria	BTR, SOD, SLD, SA, PS, SDB, DTS, NW	CSHQ	Headache + SD
8. Torres-Ferrus *et al*., 2019[13]	1619	12–18	PM	ICHD-3 beta version	DTS, insomnia	Lifestyle questionnaire	Headache
9. Lateef *et al*., 2019[14]	10,123	13–18	MwA, MwoA	ICHD-3	Insomnia	NCS-A	Headache + SD
10. Isik *et al*., 2007[15]	2228	6–13	Migraine, nonmigraine headache	ICHD-2	PS, DTS, nocturnal hyperhidrosis, snoring	Featured questionnaire	Headache + SD
11. Miller *et al*., 2003[16]	118	2–12	Migraine	ICHD (unspecified)	BTR, SLD, DTS NW, SA, PS, SDB	CSHQ	Headache + SD
12. Voci *et al*., 2021[17]	140	3–18	MwA, MwoA	ICHD-3	BTR, SLD, DTS NW, SA, PS, SDB	CSHQ, ESSCA	Headache + SD

BTR: Bedtime resistance, CSHQ: Children's Sleep Habits Questionnaire, DTS: Daytime sleepiness, ESSCA: Epworth Sleepiness Scale for Children and Adolescents, ICHD: International Classification of Headache Disorders, MwA: Migraine with aura, MwoA: Migraine without aura, *n*: Number of patients, NCS-A: National Comorbidity Survey-Adolescent, NDPH: New daily persistent headache, NW: Night waking, PDSS: Pediatric DTS Scale, PM: Probable migraine, PS: Parasomnias, SA: Sleep anxiety, SD: Sleep disorders, SDB: Sleep-disordered breathing, SDSC: Sleep Disturbances Scale for Children, SHIP: Sleep Hygiene Inventory For Pediatrics, SLD: Sleep duration, SOD: Sleep-onset delay, TTH: Tension-type headache

and Adolescents, and Sleep Hygiene Inventory for Pediatrics.[1-4,6,7,11,12] In some studies, other questionnaires, including National Comorbidity Survey-Adolescent and other nonstandardized questionnaires, were used.[3,8-10] In Table 2, we reported a synthesis of the main results of the selected 12 studies, including the statistical coefficients. In Table 3, sleep disorders of the considered studies are listed with references, to make reading easier.

Discussion and Conclusions

In our study, we selected 12 studies in the pediatric literature assessing comorbidity between headaches and sleep disorders. Seven out of 12 studies dealt with comorbidity between migraine and sleep disorders, whereas in 5 studies, only migraine was considered.

There is a bidirectional and strong relationship between headache and sleep disorders in childhood, as evidenced by multiple associations between headache features and sleep disturbances. This can be explained by many common pathophysiologic pathways. The cerebral structures, networks, and neurochemical systems that are involved in the genesis of migraine align closely with those responsible for the regulation of sleep. Critical structures and neurochemical systems for both include the cortex, hypothalamus, brain stem, glymphatic system, melatonin, orexin, serotonin, and calcitonin gene-related peptide (CGRP) transmission. Modulation of thalamocortical activity is important in both migraine and sleep.[4,19] Cortical spreading depression (CSD), which plays a key role in the pathophysiology of the attack of migraine with aura, seems to alter the quality of sleep spindle activity.[19,20] The linkage between CSD and sleep is complicated. CSD may promote restorative nonrapid eye movement sleep and could

Table 2: Synthesis of the results of the 12 selected papers

1. Main SD reported by adolescents: DTS (23.2%), insufficient sleep time (27.5%), difficulties falling asleep (40.6%), and multiple NW (38%)
Higher headache pain intensity correlated with longer SOD (r=0.26, P<0.04). Increased length of time since headache onset correlated with longer SOD (r=0.25, P<0.05). Longer time since headache onset correlated with more sleep-related problem behaviors (r=0.25, P<0.04). Higher headache pain intensity correlated with insomnia (r=0.28, P<0.02), difficulty falling asleep (r=0.24, P<0.05), and doing dangerous things without thinking (r=0.30, P<0.02). More frequent headaches correlated with more nightmares (r=0.32, P<0.007). Longer time since headache onset correlated with difficulties with morning awakenings (r=0.26, P<0.04), higher frequency of falling asleep in class (r=0.30, P<0.02), insomnia (r=0.31, P<0.01), nightmares (r=0.27, P<0.03), and unrestful night's sleep (r=−0.29, P<0.02)
2. Children with migraine have higher total score of sleep disorder symptoms (P<0.001), disorders of initiating and maintaining (P<0.001), and disorders of arousal (P<0.001) than controls. In the Pediatric DTS Scale, migraine children had higher scores (P<0.001) and a reduction in referred total sleep time mean duration (P<0.001) than controls
3. Sleep disturbances correlated with higher headache intensity (P=0.009) and longer time since headache onset (P<0.001). Sleep disturbances correlated with partial school-day absence (P=0.04), recreational activities prevented (P<0.001), and decreased functioning during recreational activities (P<0.001). Sleep disturbances correlated with daily headache disability scores (Rpb=0.35; P<0.01)
4. Sleep disturbance correlated with TTH (P=0.002) and NDPH (P<0.001). Greater sleep disturbance was correlated with higher levels of functional disability (rs≥0.16), anxiety (rs≥0.30), and depression (rs≥0.32). Higher pain levels were correlated with greater sleep disturbance among TTH patients (r≥0.23)
5. Children with headache have greater sleep disturbance than control children (P<0.001, d=1.69). Adolescents with headache suffer from greater sleep disturbance than control adolescents (P<0.001, d=1.54). Adolescents had greater sleep disturbance than children (P<0.001, d=0.58). Females had greater sleep disturbance than males (P<0.001, d=0.26)
6. Patients with migraine correlated with higher total sleep disturbance (P<0.02), sleep delay (P<0.03), and DTS (P<0.001) compared to controls. Patients with more severe migraine showed higher total sleep disturbance (P<0.01) and less SLD (P<0.03) than patients with milder headaches
7. Higher headache intensity was related to lower sleep quality in migraine patients (P<0.05)
8. 30.5% of students suffered from recurrent headaches. 28.4% of students suffered from insomnia. 35.2% of students suffered from DTS. Students with headache showed shorter sleep time (P<0.01) and nonregular sleeping habits, insomnia, DTS, and unrestful sleep (P<0.001). Prevalence of headache was higher in patients aged 16–18 years (P<0.001)
9. Adolescents with migraine had shorter SLD (P=0.022) and earlier wakeup time (P=0.002) compared to controls. Pediatric patients with headache had significantly more sleep disturbances compared to controls (ORs ranged from 2.82 to 3.77). Particularly, this involved adolescents with migraine (ORs ranged from 2.87 to 4.32)
10. Prevalence of headache: 31.4%. Prevalence of migraine: 3.3%. Prevalence of nonmigraine headache: 28.1%. The presence of nonmigraine headache correlated with snoring (P=0.01), PS (P<0.05), sweating during sleep (P<0.001), and DTS (P<0.001). Migraine headache correlated with snoring (P=0.005), PS (P=0.02), sweating during sleep (P<0.001), and DTS (P=0.004)
11. In children, headache characteristics correlated with SA (P<0.05), PS (P<0.03), BTR (P<0.03), sleepwalking (P<0.03), and bruxism (P<0.01)
12. Among patients with migraine, those with SD presented more often more than eight episodes per month when compared to children without (P=0.031). Presence of vertigo in migraine patients correlated with SD (P=0.021). 82.4% of patients with SD had migraine equivalents versus 60.5% of patients without SD (P=0.007). Total sleep disturbance was correlated with benign paroxysmal vertigo (P=0.047) and cyclic vomiting syndrome (P=0.016). Total sleep time was negatively correlated with the frequency of the attacks (r=−0.29, P<0.001). Higher CSHQ total score was linked to a higher frequency of severe attacks (r=0.21, P=0.012) and lower acute drug efficacy (r=−0.25, P=0.003). SOD correlated with high frequency of attacks (P=0.004) and the intake of acute medications (P=0.009). Low SLD correlated with frequency of attacks (P=0.005), intake of acute medications (P=0.014), and severity of migraine attacks (P=0.009). NW correlated with frequency of attacks (P=0.047) and with severe attacks (P=0.001) and negatively correlated with acute drug efficacy (P=0.008)

SD: Sleep disorders, TTH: Tension-type headache, NDPH: New daily persistent headache, OR: Odds ratio, NW: Night wakings, PS: Parasomnias, SA: Sleep anxiety, SLD: Sleep duration, SOD: Sleep-onset delay, BTR: Bedtime resistance, DTS: Daytime sleepiness

impair glymphatic flow; this has implications for possible long-term adverse effects of migraine aura with regard to the removal of beta-amyloid and tau proteins, similar to sleep deprivation.[21] The hypothalamus, so critical for the circadian rhythm, is considered to be the potential site of origin for migraine.[4,19] This is based on clinical evidence of the diurnal periodicity of migraine as well as important migraine triggers including sleep deprivation and fasting. Melatonin, a substance regulating the sleep/wake cycle, is clearly involved in the pathogenesis of cluster headaches.[22,23] Disruption of orexinergic neurotransmission has an important role in the pathogenesis of migraine beyond its involvement in the pathophysiology of narcolepsy.[19,24] Indeed, migraine is prevalent, especially among narcoleptic patients.[25] Adenosine, which is likely one of the factors involved with the homeostatic sleep drive, shows elevated levels in migraine patients.[19,26] Furthermore, exogenous administration of adenosine can trigger migraine.[27] CGRP, one of the most important neuropeptides involved in the genesis of migraine, has a role in the regulation of arousal.[19,24] In conclusion, the cerebral structures,

Table 3: Sleep disorder considered in the studies

SD	Study
Insomnia	1, 8
BTR	11, 12
Bruxism	11
Co-sleeping	11
DTS	1, 6, 8, 10
Difficulties falling asleep	1, 2
Disorders of arousal	2
Early morning awakenings	1, 9
NW	1, 2, 12
Nightmares	1
PS	10, 11
Short sleep time	1, 2, 6, 8, 9, 11, 12
SA	11, 12
Sleep disturbances	2, 3, 4, 5
SOD	1, 6, 11, 12
Sleep problems	1, 6, 12
Sleep-related problem behaviors	1, 8
Sleepwalking	11
Snoring	10, 11
Sweating during sleep	10
Unrestful sleep	7, 8

BTR: Bedtime resistance, SD: Sleep disorders, DTS: Daytime sleepiness, NW: Night wakings, PS: Parasomnias, SA: Sleep anxiety, SOD: Sleep-onset delay

networks, and neurochemical systems that are involved in the genesis of migraine align closely with those responsible for the regulation of sleep. Studies indicate that disturbed sleep is one of the most common triggers for migraine in childhood. Moreover, disturbed sleep in infancy predicts the development and persistence of headache later in childhood.[19]

Considering the clinical consequences of comorbidity between headaches and sleep disorders, it is essential to treat both diseases simultaneously. Treating only headache in a child who is also presenting a sleep disorder may not produce good results, leading to the classification of the patient as a "nonresponder" to first-line treatments. Furthermore, treating only sleep disorders in a patient with headache or other comorbidities will produce poor results. Targeting both disorders at the same time can significantly ameliorate the quality of life of patients (and their families) and reduce all symptoms and disability. Clinicians should perform the clinical evaluation of childhood headache with a careful analysis of sleep habits and sleep disturbances.

The available studies investigating the comorbidity between primary headaches and sleep disturbances in pediatric age have some methodological limitations; particularly, none of them used the International Classification of Sleep Disorders criteria to diagnose sleep disturbances.[1] Some studies even used general questionnaires not specifically designed for sleep disorders.

In conclusion, in the daily clinical practice using validated assessments for headache and sleep disorders, diagnosis is mandatory to detect this comorbidity earlier and design a better treatment strategy for the patient.

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Conflicts of interest

There are no conflicts of interest.

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