



## CLINICAL REVIEW

# Headache and sleep

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**KEYWORDS**

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**Summary** Headache and sleep have long been recognised as being interdependent due to specific causative factors. Yet, the precise understanding of the roles played by these factors in this interdependency remains elusive. Many observations have suggested a reciprocal relationship between headache and sleep; however, these hypotheses have only been partially substantiated by robust findings. Being so, additional well-designed clinical and laboratory studies are required to confirm these relationships. Nonetheless, sleep and headache are known to be related in several ways: primary headache such as migraine, cluster headache (CH) and hypnic headache (HH) can be triggered by sleep, while chronic morning headaches can be caused by sleep disorders such as sleep apnoea and insomnia. Furthermore, headache and sleep disorders can also be symptoms of other underlying pathologies. Migraine, CH and HH seems to be related to sleep stages suggesting that they may in fact be a chronobiological disorder.

Patients suffering from chronic morning or nocturnal headache should be considered for the presence of possible sleep disturbances.

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## Introduction

Headache and sleep disorders are common in the general population and often coexist in the same patient. Stress is recognised as one of the principal factors for headache and sleep disorders. Moreover, both disorders have been proven to be associated with depression and anxiety. Thus, it is plausible to conclude that headache and sleep disorders may be associated only because both are common to or symptoms of other underlying pathologies.

However, the general impression from clinical practice is that headache and sleep are in reality

more closely related. In fact, it is regularly observed that migraine attacks can be provoked by either too little or prolonged sleep time. Concurrently, migraine crises can be alleviated by the occurrence of sleep. There are also patients who complain of primary headaches with their attacks occurring predominantly during sleep or with an exclusive onset during sleep. Moreover, poor quality of sleep is frequently reported in patients with chronic headache.<sup>1</sup> Furthermore the frequency and duration of migraine attacks are reduced by a good sleep hygiene.<sup>2</sup>

All of these observations support the hypothesis of a reciprocal relationship between headache and sleep. Even so, this relationship remains misunderstood.

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Migraine, tension-type headache, cluster headache (CH) and the rare hypnic headache (HH), recently introduced in the latest international classification of headache,<sup>3</sup> are the primary headaches most frequently related to sleep. While insomnia and sleep apnea<sup>4</sup> are more commonly reported as sleep disorders which are related to headache.

## Relationship between headache and sleep

The relationship between primary headache and sleep has long been reported in literature. Rasmussen<sup>5</sup> reported a greater prevalence of sleep disturbance in patients with headache from the general population; in another study insomnia was reported to be a common symptom in patients with chronic daily headache.<sup>6</sup> Paiva et al.<sup>7</sup> identified the presence of a specific sleep disorder in 55% of subjects with onset of headache during the nocturnal sleep period. Additionally, the treatment of the underlying sleep disorders in these patients brought about an improvement in headache. Moreover, Boardman et al.<sup>8</sup> have recently found, from a general population sample, both that sleep problems are associated with all headaches and that an increase in sleep disturbance is associated with greater headache severity.

## Classifications problems

Sleep and headache appear to be inter-related in several ways. Over the last few years several classifications have been developed which have sought to better define the complex relationship between headache and sleep. Sahota and Dexter<sup>9</sup> suggested that headache may cause various degrees of sleep disruption and individualised the following types of relations between headache and sleep: (1) sleep-related headache (during or after sleep); (2) sleep-phase-related headaches (migraine, CH); (3) length of sleep and headaches and sleep relieves headaches (migraine); (4) sleep disorders and headaches (sleep apnoea, parasomnia); (5) effects of headaches on sleep; (6) dreams and headaches. More recently, Paiva and Hering<sup>10</sup> amended the above classification adding these possible clinical links between headache and sleep: (a) sleep disturbance is the cause of headache (example: morning headache as a symptom of sleep apnoea); (b) headache is the cause of sleep disturbance (example: sleep disruption induced by CH); (c) headache and sleep disorders may overlap

in the same subject or have a common cause (example: chronic tension-type headache and insomnia induced by mood disorders). Notwithstanding these headache and sleep interaction classification contributions there is no consensus regarding this topic. To demonstrate this point, presently included in the International Classification of Headache Disorders<sup>3</sup> there are only two headache types cited as being related to sleep: HH and sleep apnoea headache.

## Pathogenetic aspects

Several primary headaches such as migraine, CH and HH, are influenced by sleep stages, suggesting that hypothalamus, in particular the suprachiasmatic nucleus,<sup>11</sup> may have an important role in the pathogenetic relationship between headache and sleep. There is clear evidence for hypothalamic involvement in the pathophysiology of several primary headaches. Results from neuroendocrine studies have reported altered melatonin levels in migraine<sup>12</sup> and CH.<sup>13</sup> Peres et al.<sup>14</sup> found lowered melatonin levels in chronic migraine patients with insomnia, supporting a hypothalamic involvement in these patients. Furthermore, melatonin is effective in the prevention of migraine and CH.<sup>15</sup> Lastly, functional imaging studies have shown an activation of the hypothalamus during CH attacks.<sup>16</sup>

Additionally, the noradrenergic locus ceruleus and the serotonergic dorsal raphe are anatomical structures that are of great importance in the control of the sleep-wake cycles as well as in the modulation of pain. In particular, the serotonergic system, implicated in the regulation of sleep and in the modulation of pain, could play an important role in the relationship between headache and sleep. Serotonin is involved in the regulation of sleep and there are numerous data that demonstrate its role in the development of migraine.<sup>17</sup>

Although pathogenic mechanisms for headache and sleep have been suggested in literature, a clear model defining the relationship between headache and sleep does not exist.

## Primary headache disorders and sleep

### Migraine

Migraine is one of the most frequent neurologic disorders in industrialised countries. More commonly reported in females, typical migraine pain is: unilateral, pulsating and of moderate-severe

intensity; aggravated by physical activity and associated with nausea and /or vomiting, photo and phonophobia. Attacks last 4–72 h and in 15–20% of patients migraine is preceded by aura: a mostly visual reversible focal neurological symptom that has a duration of no longer than 1 h.<sup>3</sup>

The relationship between migraine and sleep has been known for a long time. Migraine can emerge during nocturnal sleep or following a brief period of daytime sleep. Attacks can be preceded by a lack of sleep. Sleep disturbance has been identified as one of the principal headache causes, second only to stress<sup>18</sup> and often migraine can be predicted by the length of sleep from the night before.<sup>19</sup> Sleep has also been shown to relieve migraine,<sup>20</sup> especially in children.<sup>21</sup> The relationship between migraine and sleep has also been confirmed by Kelman et al.<sup>22</sup> who found sleep complaints to be prevalent among migraineurs: over one-third of 1283 migraineurs reported difficulty initiating and maintaining a healthy sleep pattern. Additionally, a large majority of migraineurs reported sleep being an effective acute treatment. Furthermore, short sleepers exhibited significantly more frequent headaches than long sleepers and were also more likely to experience morning headaches at awakening.

In the limited number of polysomnography studies carried out to date on patients with migraine, there seems to emerge a relationship between the initiation of night-time headache and rapid eye movement (REM).<sup>23</sup> Other studies seem to evidence that migraine, present at awakening can be due to a prolonged REM from the preceding night and from stages 3 and 4 of sleep.<sup>24</sup> These data, however, were not confirmed by the study carried out by Goder et al.,<sup>25</sup> who found no alterations in the occurrence of specific sleep stages in the nights preceding a migraine attack. Gans<sup>26</sup> described a reduction in the frequency and severity of migraine attacks with the selective deprivation of the deepest stages of sleep.

A higher incidence of parasomnia has been documented in migraine patients compared with controls. From separate studies,<sup>27,28</sup> results have reported migraine patients experiencing a significantly higher frequency of sleepwalking, enuresis and pavor compared to controls.

### Tension type headache

Tension-type headache has a large prevalence in the general population with attacks lasting from 30 min to 7 days. Pain is typically bilateral, pressing and of mild–moderate intensity, not aggravated by physical activity nor associated with nausea or

vomiting. If the headache occurs more than 15 days/month for at least 6 months, the tension-type headache is chronic and in this form the presence of mild nausea is possible.<sup>3</sup>

Tension-type headache is often associated with sleep disorders.<sup>29</sup> Anxiety and depression are known to be comorbid with tension-type headache. In a study carried out on patients with chronic daily headache, insomnia was reported more frequently in patients with chronic tension-type headache while more than half of the patients who reported sleep disturbances also suffered from anxiety and depression.<sup>1</sup>

In these chronic forms, especially where there is a reported abuse of medicines, it is possible to hypothesise the existence of significant relationships among headache, sleep disorders and psychiatric disturbances.

### Cluster headache

CH is a primary headache characterised by attacks of severe unilateral retro or periorbital pain, lasting 15 min to 3 h. Attacks are associated with at least one autonomic feature and can occur up to eight times a day. CH is more common in males and heavy smokers. In the episodic form, attacks occur in clusters lasting 1 week to 1 year separated by pain-free periods.<sup>3</sup> In chronic CH (about 20% of the patients) there is no pain remission.

CH has been studied in relation to REM sleep. Dexter and Weitzman<sup>23</sup> reported that CH attacks occurs predominantly during the REM phase. While Pfaffenrath et al.<sup>30</sup> reported that the majority of CH onset attacks were rarely related to REM sleep suggesting that headache attacks were related to REM stage only in episodic CH. Being so, the correlation between CH and the various phases of sleep is still a matter of discussion. The evidence for a relationship between CH and REM sleep is in fact based on very few studies. Moreover, it is necessary to acknowledge that CHs are not always related to sleep. Riess et al.<sup>31</sup> found that only 3 of 50 patients with CH reported attacks exclusively during the night.

### Hypnic headache

HH is a rare and benign syndrome first described by Raskin<sup>32</sup> in 1988 and later Newman et al.<sup>33</sup> in 1990. Since then, over 70 cases have been reported in literature.<sup>34</sup> HH has recently been included in the International Headache Classification<sup>3</sup> and the diagnostic criteria are reported in Table 1. In this idiopathic headache syndrome, attacks only appear

**Table 1** Diagnostic criteria for hypnic headache\*

- A. Dull headache fulfilling criteria B–D
- B. Develops only during sleep, and awakens patient
- C. At least two of following characteristics:
  1. Occurs > 15 times/month
  2. Lasts  $\geq$  15 min after awaking
  3. First occurs after age of 50 years
- D. No autonomic symptoms and no more than one of nausea, photophobia and phonophobia
- E. Not attributed to another disorder

\*International Classification of Headache Disorders.<sup>3</sup>

in close temporal relationship to sleep and always awakens the patient. Pain though usually bilateral can be unilateral in up to one-third. The intensity of pain is moderate–severe with a duration usually ranging from 15 min to 3 h with attacks that can occur up to four times during the same night. Predominantly first-ever attacks present after the age of 50 and can occur more than 15 times per month. No autonomic symptoms are present, while no more than one of the following are present: nausea, photophobia or phonophobia. HH is more commonly seen in females and lithium usually provides a beneficial prevention. Good efficacy has also been reported with caffeine, flunarizine, melatonin and indomethacin.<sup>35</sup>

HH syndrome occurs only during sleep and may represent a good model for a study seeking to determine a relationship between headache and sleep. In 1988, Raskin<sup>32</sup> hypothesised that HH attacks were related to REM sleep, probably caused by an alteration of the biological hypothalamic pacemaker. Dodick,<sup>36</sup> in a polysomnography study, recorded an HH nocturnal attack in one patient during the onset of the first REM accompanied by a marked oxygen desaturation. Thus, supporting the idea that HH is most likely a REM-related phenomenon and that oxygen desaturation may play a determining role in the genesis of headache in predisposed subjects. These data have been reconfirmed in two other patients with HH.<sup>37</sup> Pat-souros et al.<sup>38</sup> recording a nocturnal attack of HH in a patient, confirmed a relation between HH and REM sleep but did not demonstrate an association with oxygen desaturation. Recently, Manni et al.<sup>39</sup> reported that, from six attacks of ten HH patients, recorded during nocturnal polysomnography, yet only two of these attacks arose from REM sleep and in no patients were breathing abnormalities found to be related. This investigation clarifies that HH attacks also occur during REM sleep. Any possible

connection between HH and breathing abnormalities still needs to be determined, as currently there is no data supporting the hypothesis that attacks are related to nocturnal desaturations.

## Sleep disorders and headache

### Insomnia

Insomnia, the most common sleep problem reported in the adult population, is defined by “a repeated difficulty with sleep initiation, duration, consolidation or quality that occurs despite adequate time and opportunity for sleep and results in some form of daytime impairment”.<sup>4</sup> Patients with insomnia are more likely than healthy subjects to complain of headache. Although the mechanism is not clear, architectural sleep changes such as frequent arousal and fragmentation of sleep are believed to be causative factors of headache in patients with insomnia. This headache type often has characteristics resembling tension-type headache, but neither specific clinical characteristics nor relationship to occurrence of awakening headache have been defined in these patients.<sup>40</sup> Moreover, insomnia is frequently comorbid with somatic and psychiatric disorders.<sup>41</sup> Patients with insomnia often complain of muscle tension, anxiety and depression. Equally, headaches like chronic tension-type headache have been shown to be associated with anxiety, depression and fibromyalgia.<sup>6,42</sup> These observations suggest a close relationship among insomnia, headache and regulation of mood and further studies are required to better understand the mechanism of these intrinsic relationships. Clinicians need to take into account a possible overlapping of these syndromes when treating insomnia patients.

### Sleep apnoea

Headache is a recognised symptom of obstructive sleep apnoea (OSA) syndrome.<sup>43</sup> In the International Classification, headache attributed to sleep apnoea is coded in the group of homeostatis disorders<sup>3</sup>; the diagnostic criteria are reported in Table 2. Headache frequency in OSA varies widely and ranges from 15% to 50% in various studies.<sup>44–46</sup> This variability may be due to study design (retrospective or prospective), the definition of headache itself or its onset. Although an association between OSA and headache has been identified, there are conflicting results in literature. Some authors have reported that headache, especially at awakening,

**Table 2** Diagnostic criteria for sleep apnoea headache\*

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- A. Recurrent headache with at least one of the following characteristics and fulfilling criteria C and D:
1. Occurs > 15 times/month
  2. Bilateral, pressing quality and not accompanied by nausea, photophobia or phonophobia
  3. Each headache resolves within 30 min
- B. Sleep apnoea demonstrated by overnight polysomnography
- C. Headache is present upon awakening
- D. Headache ceases within 72 h, and does not recur, after effective treatment of sleep apnoea
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\*International Classification of Headache Disorders.<sup>3</sup>

is more common in patients affected by OSA compared to both normal subjects and patients with other sleep disorders.<sup>47,48</sup> This type of headache is short in duration and its occurrence and severity seems to be associated with the severity of OSA.<sup>49</sup> Other authors have contested the above association concluding that a morning headache occurs in OSA just as frequently as with other sleep-related disorders and that morning headache is not a relevant symptom of OSA.<sup>50</sup> A recent finding in patients referred to specialists for headache problems, showed a percentage of OSA no higher than that reported in the general population.<sup>51</sup> Moreover, recent research has suggested that chronic morning headache is both a good indicator of severe depressive and insomnia disorders and is not specific to sleep-related breathing disorders.<sup>52</sup> On the other hand, patients having headache during the night or exclusively in the morning were diagnosed with OSA<sup>7</sup> and when the sleep disorders were treated, headache disappeared, thus giving support to an important causal relationship between OSA and headache. Finally, although morning headaches may occur in sleep disorders, this headache is not exclusively associated with this specific disturbance, as it has been observed in other non-sleep-related disorders, such as intracranial disease and arterial hypertension. Being so, the relationship between sleep apnoea and morning headache is not clear and remains controversial. Several hypotheses have been formulated to explain the relationship between OSA and the occurrence of headache at awakening: fluctuation of oxygen saturation during the night with hypercapnia, vasodilation and an increase in intracranial

pressure are all considered contributing factors.<sup>53,54</sup> Recent findings have shown that the frequency of past headache and the frequency of morning headache in the sleep laboratory are significantly increased in patients with OSA and other sleep disorders compared with healthy subjects.<sup>55</sup> Morning headaches in patients with sleep disorders were therefore concluded to be associated with both a particular shortening and fragmentation of total sleep and a reduction in total REM sleep. Furthermore, sleep disturbance, whatever its origin, leads to morning headache. Given so, it is very important to verify whether the incidence of morning headache is different from other sleep disorders. A recent study has investigated the characteristics of headache reported by OSA patients compared with insomnia patients.<sup>56</sup> This study revealed that headache is a common finding in both OSA and insomnia patients. Although headache frequency and clinical characteristics were similar in both groups, a higher frequency of morning headache was recorded in OSA patients and these headaches were also associated with disease severity. Because morning headache seems to be more specific for OSA patients than insomnia, and its occurrence appears to be related to disease severity, different pathogenic mechanisms may be hypothesised. In this study, depression was detected more frequently in insomniac patients, complaining or not of headache, compared to OSA patients. Depression in insomnia patients could also be an aggravating factor for headache.

Additionally, OSA is believed to be a trigger for migraine and CH attacks. In a first-ever study, Kudrow et al.<sup>57</sup> found a significant presence of apnoea in patients with CH. This finding has been confirmed by other authors who have reported the presence of OSA in about 80% of patients with CH.<sup>58,59</sup> Recently, Nobre et al.<sup>60</sup> found a high percentage of OSA in patients with CH. In the case of pain during sleep, most headaches occurred during the REM phase, following a desaturation episode. This risk was greater in patients over 40 years of age with a BMI > 25 kg/m<sup>2</sup>.<sup>60</sup> Some reports have seen that CH improved or disappeared when comorbid OSA is treated but the hypothesis that sleep apnoea and desaturation could be involved as triggers of CH is still to be determined. Further confirming data is required to answer these questions.

### Practice points

1. There is a reciprocal relationship between headache and sleep. Headache is both a

risk factor for sleep disorders and a consequence of sleep disorders.

2. Although an association between sleep and headache has been identified, yet, the precise influence of sleep on the development of headache remains complex and elusive.
3. Patients suffering from chronic morning or nocturnal headache should be considered for the possible presence of treatable sleep disturbance. The true relationship between morning headache and OSA can be confirmed only after headache improvement following OSA treatment.
4. Clinicians always need to thoroughly investigate for the presence of both headache and sleep disorders. A good-sleep hygiene reduces the frequency and duration of migraine. Treating chronic headache may reduce the incidence of sleep disorders.

### Research agenda

1. More well-designed clinical and laboratory studies are required to better understand the relationship between primary headache and sleep due to the undetermined roles of headache-specific and sleep-specific causative factors.
2. Migraine, CH and HH seem to be related to sleep stages suggesting chronobiological disorders. Future clinical and laboratory studies are required to confirm this.
3. Patients suffering from chronic daily headache frequently complain of sleep disorders. Few studies have examined the possible roles of an overuse of drugs in the determination of sleep disturbance.
4. Recent findings have reported that CH improves or resolves when comorbid OSA is treated, but the hypothesis that sleep apnoea and oxygen desaturation could be involved as triggers of CH is still to be determined.

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