

# Primary headaches and their relationship with sleep

## *Cefaleias primárias e sua relação com o sono*

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### ABSTRACT

There is a clear association between primary headaches and sleep disorders, especially when these headaches occur at night or upon waking. The primary headaches most commonly related to sleep are: migraine, cluster headache, tension type, hypnic headache and chronic paroxysmal hemicrania. The objective of this review was to describe the relationship between these types of headaches and sleep and to address sleep apnea headaches. There are various types of demonstrated associations between sleep and headache disorders, and the mechanisms underlying these associations are complex, multi-factorial and poorly understood. Moreover, all sleep disorders may be related to headaches to some degree; therefore, the evaluation of patients with headaches should include a brief investigation on sleep patterns and related complaints. Patients with headache at night or upon waking who are resistant to the indicated treatment require formal polysomnographic evaluation to exclude a treatable sleep disorder.

**Keywords:** headaches, migraine disorders, obstructive, pain, sleep apnea, sleep disorders.

### RESUMO

Uma clara associação é observada entre cefaleias primárias e distúrbios do sono, especialmente quando estas cefaleias ocorrem durante a noite ou ao despertar. As cefaleias primárias mais relacionadas ao sono são: migrânea ou enxaqueca, cefaleia em salvas, cefaléias do tipo tensional, cefaléia hipócnica e hemicrania paroxística crônica. O objetivo desta revisão foi mostrar a associação estes tipos de cefaleia e sono, abordando, também, a cefaleia da apneia do sono. Existem associações demonstradas e de diversos tipos entre o sono e transtornos de cefaleia e os mecanismos subjacentes a estas associações são complexos, multifatoriais e ainda mal compreendidos. Além do mais, todos os distúrbios de sono podem ter relação com a cefaleia em maior ou menor grau e, por esta razão, a avaliação do paciente com cefaleia deve incluir um breve questionamento sobre o padrão ou queixas do sono deste. Pacientes com cefaleia noturna ou ao despertar, refratários aos tratamentos indicados requerem avaliação formal com polissonografia para exclusão de um distúrbio do sono tratável.

**Descritores:** cefaleia, distúrbios do sono, dor, síndrome da apneia obstrutiva do sono, transtornos de enxaqueca.

### INTRODUCTION

A relationship between sleep and headaches has been reported in lay and scientific literature for over a century. Regulation of the sleep-wake cycle is mediated by the interaction of different neural systems and their respective neurotransmitters, components of which are shared with

pain control systems. In general, pain affects sleep and vice versa<sup>(1,2)</sup>. We found that primary headaches with no clear etiology by clinical and laboratory tests can be triggered by either short or long periods of sleep, or by interrupted or non-restorative sleep<sup>(3)</sup>. Sleep is also effective in relieving symptoms: 85% of individuals with migraine report that they choose to sleep or rest because of a headache, and many are forced to do it<sup>(4)</sup>. Therefore, headaches and sleep disturbances are common and often coexist in the same individual<sup>(3,5)</sup>, and this association is especially observed when these headaches occur at night or upon waking<sup>(6,7)</sup>.

Sleep-related headaches and the relationship between sleep and headaches are not well understood, but recent advances in the neurophysiology of sleep suggest that the biological processes behind this association lie in neuroanatomical systems common to both<sup>(5,6)</sup>. Anatomical, biochemical and physiological data support an inherent association between normal sleep physiology and the genesis of headaches in biologically predisposed individuals<sup>(3)</sup>. These data point to common pathophysiological aspects of sleep, pain (headache) and mood, which involve the hypothalamus, serotonin and melatonin<sup>(3)</sup>. Preliminary studies suggest that headaches tend to be associated with rapid eye movement (REM) sleep and an increase in the percentage of REM and slow wave sleep (SWS)<sup>(8)</sup>.

Reviews of clinical and epidemiological studies suggest a higher prevalence of sleep disorders in individuals with certain types of headaches, such as migraine, cluster headache and others<sup>(3,5,9)</sup>. In addition, chronic daily headache or headache on waking is strongly suggestive of a sleep disorder. It is estimated that 4-6% of the general population have a sleep disorder<sup>(10,11)</sup>. Studies suggest that of these individuals, approximately 18-60% are apneics and 18% are insomniacs. Mitsikostas et al.<sup>(12)</sup> identified obstructive sleep apnea syndrome (OSAS) in 29% of patients with severe headaches resistant to standard treatments.

In a recent article, we examined the prevalence of nocturnal awakening with headache (NAH) in a population in Sao Paulo, Brazil. The prevalence of NAH (at least once a week) was 8.4% in the population studied. The

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identified risk factors for NAH were: female, age of 50-59 years, obesity, anxiety, restless leg syndrome (RLS), insomnia and nightmares<sup>(13)</sup>. However, no assessment was made of headache type according to International Classification of Headache Disorders, 2nd Edition (ICHD-II)<sup>(14)</sup>.

The objective of this review is to discuss the main types of primary headache most often associated with sleep: migraine, cluster headache, tension type and hypnic headache and chronic paroxysmal hemicrania (CPH). As an exception to this proposal, we will discuss sleep apnea headache, which is the only diagnosis of headache secondary to a sleep disorder formally recognized by ICHD-II<sup>(14)</sup>. It is part of a subclassification of headaches related to hypoxia, and one of its diagnostic criteria is that it can only be confirmed after successful treatment of sleep apnea.

## PRIMARY HEADACHES RELATED TO SLEEP

### Migraine

Migraines are severe, usually unilateral headaches that commonly present symptoms such as photophobia, phonophobia, nausea, vomiting, mood disorders and sensory abnormalities<sup>(15)</sup>. They are closely related to sleep, and migraines may occur during nocturnal sleep, after brief periods of daytime sleep and upon waking. In fact, approximately 50% of migraine attacks occur between 4:00 a.m. and 9:00 a.m.<sup>(3)</sup>. In addition, sleep problems are 3 times more frequent among patients who reported having migraines<sup>(16)</sup>. The migraine crisis can be triggered by lack of sleep or sleeping too much; however, it often improves or disappears after sleep<sup>(17)</sup>. These crises are not associated with a particular sleep stage: they may occur during REM sleep or outside this period; they are more likely to occur after long periods of SWS stage and/or upon waking from REM sleep, when the patient is dreaming and has a headache<sup>(3,18)</sup>. The cyclical or periodic nature of the attacks and their relationship with cycles (sleep, menstruation, season of the year) and sunny days indicate circadian mechanisms controlled by the hypothalamus<sup>(19)</sup>.

Insomnia is among the sleep disorders most commonly related to migraine and is present in one half to two thirds of the migraine sufferers<sup>(16,17,20)</sup>. The incidence of parasomnias (sleepwalking, night terrors) is significantly higher in patients with migraine than in the general population<sup>(21)</sup>. Sleepwalking may be considered a minor criterion for the diagnosis of migraine<sup>(22)</sup>. A higher migraine frequency in narcoleptics has also been described<sup>(23)</sup>. Recent studies have identified a higher prevalence of RLS in patients with migraine<sup>(24-26)</sup>. In addition, because dopamine is involved in the pathogenesis of both conditions, this association could support the hypothetical dopaminergic imbalance in RLS and migraine, as proposed by Cologno et al. in 2008<sup>(27)</sup>.

### Cluster headache (CH)

Cluster headache pain is severe, excruciating (there are reports of it being worse than labor pain or renal colic), stabbing, puncturing, always unilateral and usually retro-orbital<sup>(28)</sup>. It is associated with at least one of the following signs on the ipsilateral side: conjunctival injection, lacri-

mation, nasal congestion, rhinorrhea, forehead and facial sweating, eyelid edema, miosis and ptosis.

Sleep has long been linked to CH. Initial observations indicated that patients frequently or always report CH onset during sleep, with pain so unbearable that it jolts the person awake<sup>(29)</sup>.

The attacks usually occur approximately ninety minutes after the patient falls asleep, coincident with the first episode of REM sleep. In fact, although data in the literature are controversial, these attacks tend to occur mostly during REM sleep<sup>(3)</sup>. The pain may also begin in stages 2 and 3 of NREM sleep, and patients may experience a reduction of REM sleep and an increase of SWS during cluster headaches<sup>(30)</sup>. The frequency of cluster headaches is one or two times per year, demonstrating their circannual nature. Moreover, the influence of sleep stages suggests hypothalamic involvement, in particular the suprachiasmatic nucleus, in the common pathophysiological processes of sleep and headache<sup>(19)</sup>.

Cluster headache patients have a high risk for OSAS, as reported in various studies<sup>(12,30,31)</sup>; polysomnography (PSG) is necessary in patients with cluster headaches resistant to usual treatment<sup>(32-34)</sup>.

A case study monitoring a patient with cluster headaches over a 9-week actigraphy recording and repeated PSG showed acute sleep-wake pattern changes and REM sleep abnormalities, both of which diminished after the episode<sup>(35)</sup>. The authors concluded that in this patient, the CH was associated with poor regulation of the sleep-wake cycle, involving the biological clock and alertness mechanisms, particularly in REM sleep; all of these abnormalities were consistent with alteration of the posterior hypothalamus<sup>(35)</sup>. Studies using positron emission tomography support this conclusion<sup>(36)</sup>. Moreover, the efficacy of lithium treatment has been shown to involve the hypothalamus, resulting in selective accumulation and stabilization of serotonin in the central nervous system, causing inhibition of REM sleep and circadian rhythm changes<sup>(3)</sup>.

### Tension-type headaches

Tension-type headaches can be episodic or chronic. Diagnosis of episodic cases requires a history of the last 10 headaches that lasted from 30 minutes up to 7 days, and at least 2 of the following features: feelings of pressure/squeezing; weak or moderate intensity; bilateral; not aggravated by physical activity. Neurological and clinical examinations must be normal<sup>(14)</sup>. Nausea, vomiting, photo- and phonophobia exclude a diagnosis of tension-type headaches.

Chronic tension-type headaches occur more than 15 days per month (or more than 180 days per year) and may have one (but no more) of the following features: mild nausea, photo- and phonophobia<sup>(14)</sup>.

Insomnia has been linked to chronic headaches and may worsen the prognosis for tension-type headaches<sup>(31)</sup>. Hypersomnia, nocturnal bruxism and RLS are associated with greater headache frequency, especially for tension-type headaches. Sleep fragmentation and/or increased muscle activity during sleep is the likely mechanism in

these patients<sup>(37)</sup>. Data supporting this hypothesis come from PSG in patients with tension-type headaches that showed frequent awakenings and reduced SWS<sup>(38)</sup>.

### Hypnic Headache

Hypnic headache is a rare type of primary chronic headache occurring exclusively during sleep, usually in people over 50 years of age, and its pathophysiology has not been clearly established<sup>(39,40)</sup>. It is characterized by mild to moderate pain that wakes the patient. These headaches occur more than 15 times per month and last 15-180 minutes<sup>(13)</sup>.

It is the only type of headache that is strictly related to sleep (both day and night) and wakes the patient. Therefore, it is also called "alarm clock headache"<sup>(3,40)</sup>. Case reports suggest a relationship between waking and headaches during slow-wave sleep<sup>(41,42)</sup>, REM sleep or during nocturnal desaturations<sup>(43)</sup>. The relationship to REM sleep may be false because headaches that wake the patient during REM may have started in another stage<sup>(44)</sup>. Studies using laser-evoked pain potentials showed a late positive component recorded in stages 2 and REM, and its amplitude is significantly higher in trials followed by awakening<sup>(45)</sup>. In contrast, Bentley et al.<sup>(46)</sup> demonstrated that higher thermal stimulus intensity is necessary to awaken from slow-wave and REM sleep compared to stage 2. However, when individuals are woken abruptly during the REM sleep stage, the perception of pain is reduced by sleep inertia, which does not occur when they are woken in stage 2 or SWS<sup>(47)</sup>.

Because hypnic headaches usually begin after the fifth or sixth decade of life, their pathophysiology may be associated with age-related changes in sleep patterns, such as more frequent awakenings and a marked reduction of SWS, as described for tension-type headaches<sup>(3)</sup>. An association with hypothalamic dysfunction is considered an important pathophysiological mechanism for this type of headache, because waking implies dysregulation of the sleep/wake cycle<sup>(48)</sup>. This type may also be related to reduced melatonin, but it is important to note that melatonin secretion is also reduced in other primary headaches including migraine and cluster headache<sup>(49)</sup>.

### Chronic Paroxysmal Hemicrania (CPH)

CPH is a rare syndrome that usually manifests as a relatively brief unilateral attack of severe pain, followed by trigeminal-autonomic symptoms. These attacks occur abruptly several times a day. The pain occurs mainly in the ophthalmic trigeminal region, but other parts of the head can be affected<sup>(14)</sup>. There is no preferred time of day when this type of pain begins, but when it occurs during sleep, it is usually associated with REM. In this way, the attacks are like cluster headaches, which are very similar, clinically<sup>(50)</sup>.

### SECONDARY HEADACHES RELATED TO SLEEP: MORNING HEADACHES

In the ICHD-II, headache attributed to sleep apnea has the code 10.1. within the group of headaches attributed to homeostasis disorders<sup>(14)</sup>. The diagnostic criteria include recurring headaches that are present on awakening and

disappear after effective treatment of sleep apnea. Sleep apnea headaches have the following features: occur more than 15 days per month; pain or bilateral pressure not accompanied by photophobia or phonophobia; resolved within 30 minutes; confirmation of sleep apnea by all-night PSG<sup>(14)</sup>.

Some studies have reported a strong association between morning headaches, OSAS<sup>(51,52)</sup> and snoring<sup>(52-54)</sup>. However, epidemiological studies have shown that this type of headache is not specific to sleep-related breathing disorders<sup>(55)</sup>. In a study by Goder et al.<sup>(56)</sup>, verification of the PSG findings on the night preceding morning headaches included a reduction in total sleep time, sleep efficiency and the amount of REM sleep and an increased number of awakenings. Complaints of morning headaches are also reported at a rate 3-5 times higher among patients who suffer from RLS<sup>(57)</sup>.

### RELATIONSHIP BETWEEN NOCTURNAL AWAKENING WITH HEADACHE AND SLEEP DISORDERS

There are few studies examining the relationship between NAH and sleep disorders. Evans et al.<sup>(58)</sup> reported that headaches that wake a person during the night are due to interrupted sleep or one of the following underlying processes that interrupt sleep: OSAS or nocturnal hypoxia/hypercapnia, RLS or periodic movements during sleep, psychophysiological insomnia and depression/anxiety. In our epidemiological study of sleep disorders in São Paulo, NAH was associated with insomnia, RLS, bruxism and nightmares, but not with sleep apnea<sup>(13)</sup>.

### INVESTIGATION WITH PSG

A physician who examines a patient presenting with headaches can take advantage of this auxiliary test. It is particularly useful when confronted with nocturnal headache or unusual awakening in the context of ICHD-II in the absence of a psychosocial disorder or abuse of analgesics and with a clinical history suggestive of sleep disorders<sup>(33)</sup>. PSG is also indicated in suspected cases of sleep-related respiratory disorder, narcolepsy and parasomnias. Diagnosis of insomnia is usually based solely on clinical history<sup>(29)</sup>.

For well-defined primary headaches, it is possible to waive a formal sleep study<sup>(29)</sup>. As previously mentioned, PSG may be necessary in patients with cluster headache resistant to treatment<sup>(33)</sup>.

### CONCLUDING REMARKS

It is important to emphasize and consider possible neurobiological associations between sleep and headaches. For example, the hypothalamus is an important brain region that facilitates sleep (anterior part) and maintains wakefulness (posterior part). In addition to other hypothalamic functions, such as homeostasis and pain control, its effects on the transition from wakefulness to sleep or vice versa may play a role in the mechanisms of headache<sup>(59)</sup>.

Moreover, the association of symptoms of depression and stress with many headache cases is explained in part by actions of the serotonergic system, which is com-

mon to sleep, headache and pain and is located primarily in the locus coeruleus and dorsal raphe nucleus<sup>(60)</sup>.

In this brief review, we emphasized the following aspects: - there are several demonstrated associations between sleep and headache disorders; -the mechanisms underlying these associations are complex, multi-factorial and still poorly understood; - all major sleep disorders are related to headache to some degree; - primary headache disorders affect sleep or are directly related to sleep disorders and performance throughout the day; - all assessments of patients with headache should include questions about sleep patterns and related complaints; - and patients with headache at night or upon waking, who are resistant to prescribed treatments, require formal PSG evaluation to exclude a treatable sleep disorder.

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