Migraine and sleep deprivation: integrative review

Migrânea e privação do sono: revisão integrativa

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ABSTRACT

BACKGROUND AND OBJECTIVES: Migraine is a type of primary headache, and its pathophysiology remains incomplete. The relationship between sleep and migraine is easily identified by migraine patients. The aim of this review was to investigate the relationship between sleep deprivation and migraine.

CONTENTS: A search was made for articles using the terms: "migraine" and "sleep deprivation" in the Pubmed, *Biblioteca Virtual da Saúde* (Virtual Health Library - LILACS and IBECS) and Scielo databases. The first analysis was based on title and abstract. In cases where the title and abstract were not clear, the article was accessed in its entirety. After applying the exclusion criteria, 49 articles remained. These articles were analyzed and organized into two tables: one for articles that treated sleep as a trigger and the other for articles that explored the pathophysiological relationship between sleep and migraine.

CONCLUSION: It is possible that sleep deprivation causes or worsens migraine crisis due to its ability to cause oxidative stress in the brain. This in turn activates TRPA1 receptors located on first-order trigeminal neurons. Activation of these receptors initiates the sensitization process of the trigeminal system that culminates with the antidromic release of calcitonin gene-related peptide in the dural afferents of these neurons in the trigeminal ganglion. The relationship between insomnia and migraine seems to converge with this same pathophysiological process, since sleep deprivation imposed by insomnia would be able to generate a migraine crisis through increased oxidative stress.

Keywords: Headache, Migraine disorders, Sleep deprivation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Migrânea é um tipo de cefaleia primária e sua fisiopatologia permanece incompleta. A relação entre o sono e a migrânea é facilmente identificada pelos pacientes migranosos. O objetivo deste estudo foi investigar a relação entre privação de sono e a migrânea.

CONTEÚDO: Foi feita uma busca por artigos utilizando os termos: "*migraine*" e "*sleep deprivation*" nas bases de dados Pubmed, Biblioteca Virtual da Saúde (LILACS e IBECS) e Scielo. A primeira análise foi feita com base no título e no resumo. Nos casos em que o título e o resumo não foram esclarecedores, o artigo foi acessado na íntegra. Após a aplicação dos critérios de exclusão, restaram 49 artigos. Estes artigos foram analisados e organizados em duas tabelas: uma destinada aos artigos que tratavam o sono como um gatilho e a outra com artigos que exploravam a relação fisiopatológica entre sono e migrânea.

CONCLUSÃO: É possível que a privação do sono provoque ou agrave as crises de migrânea devido a sua capacidade de causar estresse oxidativo no cérebro, que ativa receptores TRPA1 localizados nos neurônios trigeminais de 1ª ordem. A ativação destes receptores inicia o processo de sensibilização do sistema trigeminal que culmina com a liberação antidrômica de peptídeo relacionado ao gene da calcitonina nos aferentes durais destes neurônios no gânglio trigeminal. A relação da insônia com a migrânea parece confluir para este mesmo processo fisiopatológico, já que a privação de sono imposta pela insônia seria capaz de gerar a crise migranosa através do aumento do estresse oxidativo.

Descritores: Cefaleia, Privação do sono, Transtornos de enxaqueca.

INTRODUCTION

Migraine is a type of primary headache that happens episodically or chronically. Symptoms typically manifest for 4 to 72h and can be disabling. Pain is usually unilateral, pulsatile, worsens during physical efforts, and is accompanied by symptoms such as nausea and sensitivity to light, sound, or odors. Auras occur in about 25% of patients, usually just before the onset of headache. The diagnosis is primarily clinical, and treatment involves triptans, dihydroergotamine, antiemetics, and analgesics. Prevention measures include lifestyle modifications and drugs.

The pathophysiology of migraine remains unclear although numerous theories have been proposed. The pathophysiological hypothesis began with the vascular theory of migraine proposed in 1940[1]. In the 1980's, the sterile neurogenic inflammation theory appeared, in which there would be an activation of nociceptive fibers that innervate the meningeal vessels. This hypothesis has

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been widely developed, and today the participation of peripheral and central sensitization of the trigeminocervical complex in the pathophysiology of migraine has been established[2].

Recent studies have brought new perspectives on the heredity, anatomical and functional characteristics, and pharmacological mechanisms of the drugs used so far. The recognition of the role of neuropeptides has a special relevance, such as the calcitonin gene-related peptide (CGRP), in the onset of a migraine attack[3]. Although there is evidence in favor of a peripheral origin in the sensitization of trigeminal afferents, other evidence suggests that the genesis of the migraine crisis is found in the central nervous system and involves a dysfunction of the neurons of the brainstem and hypothalamus[4].

In this perspective, Goadsby et al.[5] analyzed extensively the hypothesis of dysfunction of hypothalamic and brainstem neurons responsible for important aspects of body homeostasis and sensory processing. In this study, migraine is a sensory processing disorder, and the most evident argument for this statement is the fact that, for migraineurs, usual sensory stimuli are interpreted as exacerbated, usually considered "triggers" in the deflagration of a migraine attack. This observation conciliates hereditary factors with the susceptibility to the environment and exposure to stimuli, which is characteristic of individuals with migraines. Therefore, it's evident that items essential to homeostasis, typically regulated by hypothalamic circuitry, such as hunger and sleep, are also important triggers of migraine.

The relationship between sleep and migraine is easily identified by migraine patients. In fact, 5% of non-migraineurs also report that excessive sleep, or lack of it, is related to the onset of a headache[2]. Furthermore, for many individuals, sleep is capable of relieving or solving a migraine crisis[6]. In addition, chronobiological patterns are observed for the onset of pain. It's common for migraine patients to have a typical time for their crisis, for instance, waking up in the early morning hours due to pain[7].

A strong association between sleep disorders and migraine is also observed[8-11]. Such association is noticed even in the pediatric population[12]. Thus, it's quite coherent that the treatment, whether pharmacological or through behavioral changes, of sleep disorders is recommended as a first-line treatment for primary headache disorders[13,14]. Behavioral changes in daily life habits, such as the rhythm of sleep and wakefulness, although difficult to implement, seem to be a successful strategy.

Considering that insomnia is the most frequent sleep disorder in the population, and in light of the current understanding of migraine pathophysiology, it's reasonable to establish a bidirectional relationship between sleep and headache in which sleep alterations trigger headache, and the latter, in turn, affects the quality and quantity of sleep[15,16]. If sleep regulation itself may be compromised in migraine patients, then it's possible that insomnia, so often reported by them, is not the cause of a migraine crisis, but rather, the prodrome of an upcoming crisis.

The objective of the study was to investigate the relationship between sleep deprivation and migraine, understanding that insomnia in migraine patients may be part of the set of changes that precede a migraine crisis. This review will also try to identify possible pathophysiological mechanisms by which sleep deprivation increases the intensity and/or frequency of migraine attacks.

CONTENTS

The search was carried out in the Pubmed, *Biblioteca Virtual da Saúde* (Virtual Health Library - LILACS and IBECS) and Scielo databases using the terms: "migraine" and "sleep deprivation". No filters were used. The time frame was from 1980 onward, and the search resulted in 74 articles. A manual selection from the references of the review articles found in the initial search was also made. The manual selection, as described, resulted in another 24 articles, totaling 98 articles. Of these 98 articles, 8 were duplicates and were therefore excluded.

For the 90 collected articles, a selection based on title and abstract was made by consensus among the authors. In cases when the title and abstract were unclear, the articles were accessed in full. All articles that exclusively involved a population under 18 years of age, articles that dealt with specific forms of migraine, such as familial hemiplegic migraine, articles that dealt with animal studies, letters to the editor, or articles that evaded the question of interest were excluded, resulting in the exclusion of 41 articles (Figure 1).

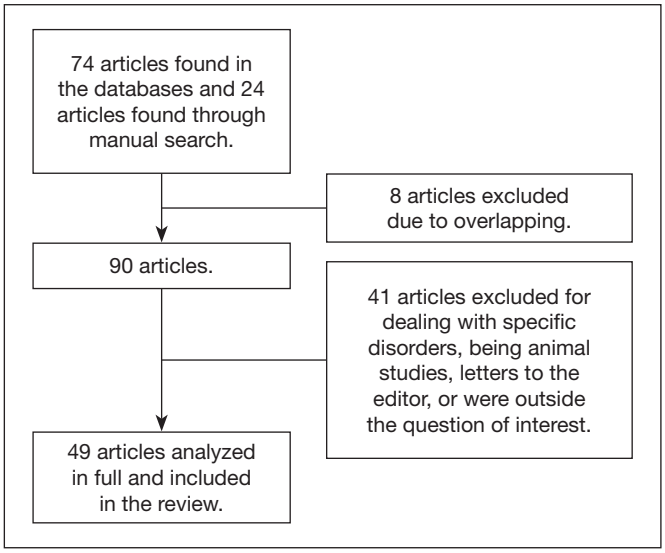

Figure 1. Articles selection flowchart

The 49 remaining articles were read in full, and this analysis showed that they could be divided into two groups: approximately half of the articles addressed the issue in an essentially epidemiological way, i.e., they argued that sleep deprivation is a frequent trigger for headache and aimed to sort out the various triggers in a given population; the other half of articles involved some kind of experimentation, i.e., sleep deprivation was investigated through complementary tests, such as polysomnography (PSG), and aimed to answer questions about the sleep characteristics and the impact of sleep deprivation on migraine patients.

RESULTS

Therefore, the first group of articles was gathered in table 1 and the second group of articles in table 2.

Table 1. List of articles analyzed regarding the presence of the term "sleep" as a trigger for migraine

Authors	Sleep as trigger
Rasmussen[17]	Sleep deprivation or decreased sleep functions as a trigger for both migraine and TTH patients.
Robbins[18]	Poor sleep or not enough sleep are considered triggers for migraine patients, whereas few patients identify oversleeping as a trigger for their attacks.
Turner et al.[19]	Fatigue and sleep are more relevant triggers for men than women.
Alders, Hentzen and Tan[20]	Sleep deprivation is a frequent trigger for both migraine and TTH.
Chabriat et al.[21]	Fatigue and sleep alterations are the most frequent triggers in both migraine and non-migraine populations.
Bánk and Márton[22]	Sleep deprivation is one of the most common triggers of migraine with and without aura.
Spierings, Ranke and Honkoop[23]	Sleep deprivation is one of the main triggers for migraineurs and especially for TTH patients.
Ierusalimschy and Moreira Filho[24]	Sleep deprivation is one of the main triggers in migraine patients, whereas oversleeping is infrequently reported.
Zivadinov et al.[25]	Sleep disturbances are frequent triggers in TTH patients and with more relevance in migraine patients.
Karli et al.[26]	Sleep alterations are the most frequent triggers for migraineurs, individuals with typical aura without headache, and TTH patients.
Wöber et al.[27]	Sleep deprivation and change in nightly habits are not identified as relevant triggers in the general population when compared to patients in specialized outpatient clinics.
Kelman[28]	Poor quality sleep is a trigger for migraineurs. Some patients identify sleeping late as a trigger.
Fukui et al.[29]	Sleep alterations are frequent triggers in migraineurs.
Bokhari et al.[30]	Sleep deprivation is the most common trigger in migraineurs. Sleep is a frequent relief factor for them.
Andress-Rothrock, King and Rothrock[31]	Poor sleep or not enough sleep are considered triggers for migraine patients.
Yadav, Kalita and Misra[32]	Sleep deprivation is a common trigger in Indian migraineurs when compared to other populations.
Carod-Artal et al.[33]	Sleep deprivation is one of the most frequent triggers in Brazilian and Spanish migraineurs, with higher prevalence in the Brazilian population.
Haque et al.[34]	Sleep deprivation is more common as a trigger in migraine than in TTH. However, sleep is a similar relief factor for both migraine and TTH.
Wang et al.[35]	Sleep alterations are the main trigger among migraineurs, while among TTH patients it's the second trigger.
Iliopoulos et al.[36]	Sleep deprivation is one of the most common triggers for migraine, with or without aura, and TTH. Oversleeping is a more frequent trigger in individuals suffering from migraine with aura.
Park et al.[37]	Sleep deprivation is one of the most frequent triggers in episodic migraine.
Peris et al.[38]	Non-adequate sleep is one of the main triggers for migraineurs.
Lisicki et al.[39]	On average, migraineurs have four different triggers, with sleep deprivation being one of them.
Portela et al.[40]	Sleep deprivation is one of the most common triggers in the college students population studied, similarly to the general population.
Tai et al.[41]	Regardless of geographic location, sleep deprivation is one of the main triggers for migraine and TTH.

TTH = tension-type headache.

Table 2. List of articles analyzed regarding sleep deprivation and its relationship with migraine

Authors	Objectives and Methodologies	Results	Conclusions
Blau[2]	Analyze the hypothesis that migraine is a primary neurological disorder with secondary vascular manifestations.	Sleep, besides being a trigger for migraine, may also be a way to resolve crisis. In addition, sleepiness is considered a symptom of migraine.	It's proposed that specific sensory areas of the cortex and hypothalamus may act as areas where a migraine attack is initiated.
Sahota and Dexter[6]	Assess the association between sleep and headaches.	Migraine seems to be associated with an increase in REM sleep and stages III and IV of non-REM sleep. This association is related to sleep quality rather than the circadian rhythm. A period of sleep may resolve the crisis.	Given the close anatomical and neurochemical associations between headache and sleep, it's feasible to consider the existence of a common substrate for these two phenomena.

Continue...

Table 2. List of articles analyzed regarding sleep deprivation and its relationship with migraine – continued

Authors	Objectives and Methodologies	Results	Conclusions
Inamorato, Minatti-hanntjch and Zukerman[42]	Clarify the relationship between migraine and sleep.	Patients report that sleep can affect them in one or several ways. When only one way was reported, relief was the most frequent. For those who report multiple ways of interaction, migraine attacks may be triggered by sleep deprivation or sleep excess.	Patients identify that sleep affects them in a single or multiple ways, this suggests that there are multiple pathophysiological mechanisms contributing to the crisis.
Kelman and Rains[43]	Examine sleep complaints in relation to headache frequency and severity.	Headache is triggered by sleep deprivation or excessive sleep. Sleep can also be a relieving factor. Migraineurs with few hours of sleep (<6h) have more frequent and intense headaches than migraineurs with more hours of sleep and are more likely to have morning episodes.	The group that doesn't get enough sleep exhibits a more severe and frequent pain pattern. Sleep complaints occur more frequently among patients with chronic headache.
Calhoun and Ford [13]	Evaluate the impact of BSM on chronic migraine in women.	The group undergoing BSM report a reduction in headache frequency and intensity. Those who sleep less are more likely to transform migraine chronic to episodic	Behavioral sleep intervention was associated with improvement in headache frequency and intensity, as well as making attacks sporadic.
Gallup and Gallup[44]	Evaluate the physiological substrate of yawning on thermoregulation.	In rats, prolonged sleep deprivation has been shown to increase brain temperature, which causes yawning.	Migraine has been associated with thermoregulatory dysfunction and atypical yawning. This mechanism could explain the relationship between sleep deprivation and the onset of a migraine attack.
Rains[7]	Discuss the nature and prevalence of sleep complaints in patients with migraine.	In most cases, insomnia preceded migraine. Chronic insomnia is significantly related to headache. Sleep dysregulation can cause or reduce headache thresholds.	Insomnia is the most common sleep disorder in patients with headache. Recent evidence suggests that migraine can be relieved with better sleep regulation, either by drug or behavioral therapy.
Yeung, Chung and Won [45]	Assess the frequency of headache, sleep difficulties, mood disturbances, and functional impairment in women through a self-administered questionnaire.	Women with headache are significantly more likely to report symptoms of insomnia than those without headache. The prevalence of these symptoms is uniform among women with unspecified headache, TTH, and migraine.	The association between insomnia and headache is more evident as the number of headache episodes increases. Middle-aged women with symptoms of anxiety, depression, and sleep disturbances are at increased risk for headache.
Lovati et al.[15]	Review the anatomy and physiology of sleep disorders associated with perceived headache.	Sleep quality is related to the presence of allodynia associated with migraine.	Sleep disorders may favor central sensitization of the trigeminal nucleus causing allodynia, which in turn may undermine sleep.
Lateef et al.[16]	Assess whether migraine differs from non-migraine headache in terms of insomnia and the severity of sleep disturbances.	Adults with headache report greater difficulty in: initiating sleep, staying asleep, and waking up early in the morning. In addition, they have more fatigue during the day.	Adults with headache have a greater risk of developing sleep disturbance regardless of the type of headache.
Houle et al.[46]	Evaluate the relationships between stress, sleep duration, and headache in patients with chronic headaches (migraine or TTH).	Two consecutive days of high stress or not enough sleep were strongly predictive of headache, whereas two days of low stress or adequate sleep were protective.	Headache risk increases proportionally with high stress and low sleep: these are strongly correlated and impact one another.
Tran and Spierings[8]	Summarize the current scientific literature concerning the nature of the headache-insomnia relationship.	Headache is more associated with insomnia than vice versa. The association between insomnia and headache is more common in severe insomnia.	Insomnia is a risk factor for headache. Patients with TTH and migraine should be routinely evaluated for insomnia.
Engstrom et al.[47]	Compare subjective and objective sleep quality through diaries and PSG with headache in migraine.	PSG of patients with migraine, in the inter-crisis period, shows signs of sleep deprivation although there are no objective differences in the amount of sleep.	Migraine patients show relative sleep deprivation and need more hours of sleep than controls.

Continue...

Table 2. List of articles analyzed regarding sleep deprivation and its relationship with migraine – continued

Authors	Objectives and Methodologies	Results	Conclusions
Engstrom et al.[48]	Compare subjective and objective sleep quality through diaries and PSG in patients with SM and NSM.	SM patients present migraineurs crisis during sleep or upon awakening; whereas NSM patients present crisis throughout the day. Only NSM patients show evidence of sleep deprivation in PSG.	Signs of sleep deprivation characteristic of migraine patients in the inter-crisis period are evident only for patients whose crises occur randomly during the day.
Engstrom et al.[49]	Compare subjective and objective sleep quality through diaries and PSG in SM, NSM and TTH patients.	Although the number of hours of sleep is adequate, the TTH and NSM groups have PSG with evidence of sleep deprivation.	NSM and TTH patients show greater similarity to each other as they require more hours of sleep than SM and controls. SM patients show more sleep disturbances than controls.
Walters, Hamer and Smitherman[50]	Quantify the relationships between sleep disturbances and headache-related variables in patients with episodic migraine.	Patients with episodic migraine report poorer sleep quality.	Poor sleep quality is associated with episodes of migraine and this relationship cannot be attributed exclusively to comorbidities such as depression and anxiety.
Stark and Stark[9]	Evaluate the relationship between chronic headache and sleep disorders, especially OSA.	In addition to OSA, migraine may also be related to parasomnias, restless legs syndrome, daytime sleepiness, poor sleep quality, and insomnia.	There is a clear association between OSA and snoring with morning headache. OSA and chronic migraine share obesity and patent foramen ovale as possible comorbidities.
Borkum[51]	Present the available literature on the capacity of migraine triggers to generate oxidative stress in the brain.	The TRPA1 receptor, present in C-type fibers, can be activated by oxidative stress, promoting CGRP release and triggering neurogenic inflammation. Except for pericranial pain, the other common triggers of migraine, including sleep deprivation, are capable of generating oxidative stress.	Sleep deprivation is associated with depletion of reduced glutathione in the brain, so it's capable of generating oxidative stress, triggering neurogenic inflammation and headache.
Woldeamanuel and Cowan [52]	Evaluate the occurrence of episodic and chronic migraine in patients who maintain and those who do not maintain a regular lifestyle.	Patients with chronic migraine had a less regular lifestyle than patients with episodic migraine.	A regular lifestyle characterized by exercise, standardized meal times, adequate hours of sleep, and hydration status prevent chronic migraine.
Kim et al.[53]	Evaluate the occurrence of insufficient sleep in three groups of subjects: without pain, with non-migraine pain, and with migraine.	Insufficient sleep is most frequent in the respective order: migraineurs, patients with non-migraine pain, and lastly, patients without pain.	The average sleep time reported was equal in all three groups, so it's assumed that migraineurs need more hours of sleep to feel rested.
Rosenberg, Butler and Seng[14]	Analyze lifestyle habits in people with episodic migraine.	Recent studies suggest that individuals with episodic migraine have poor quality sleep that influences the frequency and severity of pain.	Episodic migraine appears to be more associated with sleep quality than with sleep duration.
Song et al.[54]	Correlate the frequency and intensity of migraine episodes with the duration and quality of sleep.	Headache intensity is similar in migraineurs who sleep < 6 h or > 6 h. However, in migraineurs who sleep < 6 h, there is a higher frequency of episodes.	Short self-reported sleep duration (< 6 h) is associated with an increase in headache frequency.
Bertisch et al.[55]	Temporally correlate sleep quality with migraine attacks.	Low sleep efficiency is related to a higher risk of headache on the second day after the evaluated night.	Low sleep efficiency appears to increase the risk of migraine onset from 48 hours following the period of compromised sleep.
Navarro-Pérez et al.[56]	Evaluate the effect of 24-hour on-call shifts on disability caused by headache.	Among doctors with migraine, disability increased from little or none to moderate disability after six months, along with worsening depressive and anxious symptoms.	It's not possible to conclude whether the increase in headache disability is due to sleep deprivation or to worsening depressive and anxious symptoms.

TTH = tension-type headache; PSG = polysomnography; OSA = obstructive sleep apnea; BSM = behavioral sleep modification; SM = sleep migraine; NSM = non-sleep migraine.

DISCUSSION

The epidemiological studies developed over the period covered in this review (Table 1) allow us to observe the high frequency which sleep is mentioned as the agent responsible for migraine. Several studies propose to evaluate the main triggering factors of a migraine attack. Migraineurs have, on average, 4 triggers[39], among which the most frequently mentioned are stress, prolon-

ged fasting, climatic changes, fatigue, menstruation, and sleep deprivation.

Sleep deprivation is even cited as the most prevalent trigger[36] and sometimes as the second most prevalent trigger[20,22]. However, it's usually described between the third and fourth position of prevalence[18,37,38,40]. It's important to mention that such a relationship is found both in migraines with aura and without aura[36], as well as in chronic and episodic migraines[37].

Sleep deprivation is a common trigger for migraine and tension-type headache (TTS)[35,36,41]. However, individuals with this type of headache present triggers less frequently than migraineurs, although sleep also appears as one of the main factors[35].

On the other hand, sleep, besides being able to precipitate a crisis, can also be a relief factor[30,34], being a strategy used by both migraineurs and TTH patients. Thus, the suggestion is that there are distinct roles for sleep in the pathophysiology of migraine.

Table 2 presents a diversity of approaches to the relationship between sleep deprivation and migraine. Some studies treat the term "sleep deprivation" as an involuntary condition caused by the individual's work activity[46,56]. Most studies, however, use the term as an effect of or synonym for insomnia[7,8,13,16,45,50].

Insomnia is a complaint of having difficulty to fall asleep or staying asleep and, therefore, involves some degree of subjectivity[57]. In general, the subjectivity falls on the aspect of how many hours of sleep are necessary for an individual to perceive that period as adequate.

Some studies approach the question in a quantitative way, i.e., by hours of sleep[43,54]. The concomitant use of sleep diaries or questionnaires that evaluate sleep quality increases the quality of these studies, making it easier to analyze what is sleep deprivation due to work activity and what is insomnia.

One way to approach the sleep-migraine relationship is through PSG performed in migraine patients[6]. A Sahota and Dexter showed a consistent association between morning migraine crisis and an earlier sleep period, with increased volume of non-REM III and IV sleep and, especially, REM sleep: this situation of the morning headache in which, in general, the patient is awakened by pain, is consistent with the physiological architecture of sleep in which an increased amount of REM sleep is already observed at the end of a night's sleep. These changes in the sleep pattern of migraineurs, especially in the two nights before a migraine crisis, suggest a dysfunction in the neuronal structures involved in sleep regulation, making the hypothalamus and the brainstem possible crisis triggers[15].

Later, another study observed that the increase in REM sleep periods and in non-REM sleep periods III and IV is equivalent to the sleep rebound found in healthy individuals when deprived from sleep[58]. In addition, these researchers identified two groups of migraineurs: those who are awakened by pain, called "sleep migraineurs" (SM), and those who present headache at any time of day, called "non-sleep migraineurs" (NSM). Only NSMs show signs of sleep deprivation on PSG. Authors have also studied patients with TTH and observed that these patients resemble NSMs and differ from controls and SMs, despite sleeping the same amount of hours. These evidence of sleep deprivation in the NSM and TTH groups suggest that these individuals need more hours of sleep to not show daytime sleepiness and consequently, not show signs of sleep deprivation on the PSG[47-49].

In this same perspective, Kim et al.[53] showed that insufficient sleep is more frequent in migraineurs, non-migraine pain patients, and pain-free individuals, respectively. The average sleep time reported was the same in the three groups, therefore reinforcing the idea that migraine patients need more hours of sleep to consider it as sufficient.

In fact, its low efficiency is related to a higher risk of headache on the second day after the evaluated night[55]. When sleep is considered short and associated with stress, the risk of headache increases[46].

One can evaluate more objectively the studies that analyze the amount of hours slept by the patients. Migraine patients who sleep less than 6 hours per night have more frequent and more intense headaches than those who sleep more hours, besides being more prone to present morning episodes[7,28,45,54]. In addition, migraineurs who have a shorter sleep time may present crises with increased intensity[43].

However, for other authors, quality is more important than duration of sleep, in such a way that poor quality sleep influences the frequency and severity of pain in cases of episodic migraine[14]. In that sense, behavioral strategies, called sleep hygiene, which increase the migraine patients' amount of hours slept and quality of sleep, have shown to be effective in reducing the frequency and intensity of crises[13,14]. Even though there is no complete reduction of the condition, behavioral strategies are capable of transforming chronic migraine into episodic migraine. Another study has shown that a regular lifestyle, characterized by physical exercise, standardized mealtimes, adequate hours of sleep, and hydration status avoids chronic migraine[52].

The influence of a good night's sleep on migraine is so great that the use of sleep-inducing drugs is justified[7]. It seems that optimizing a migraine patient's sleep during the night, either behaviorally or pharmacologically, may prevent the "rebound effect" of this relative sleep deprivation found in these individuals, which is probably involved in the genesis of headache.

Several articles associate migraine headache with insomnia without being able to establish a cause-and-effect relationship[7-9,16,45]. That is, migraine or non-migraine headache increases the risk for the onset of insomnia, just as insomnia increases the risk for the onset of headache.

Insomnia and migraine can be considered comorbidities in relation to anxiety and depression[45,50,56], but it's not possible to establish a cause-and-effect relationship. On the other hand, the sum of these diagnoses increases the frequency and intensity of migraine attacks, increasing the risk of an episodic headache to be transformed into a chronic headache.

What has been exposed so far by the analysis of the various studies is coherent with the idea of a bidirectional relationship between migraine and sleep, and with the involvement of the hypothalamus in migraine pathophysiology[2,4,15,16]. The specific mechanism by which sleep deprivation causes headache remains a subject of further studies, with authors proposing new hypotheses in an attempt to understand it[52].

Gallup[59] presented the hypothesis that yawning (a physiological event present in all mammals and associated with sleepiness) has a thermoregulatory function in the brain. According to this hypothesis, the physical act of yawning alters two conditions: the temperature of the blood flowing to the brain, and the speed in which that happens. The intense opening of the jaw forces blood through blood vessels away from the head, which increases the speed in which fresh blood flows to the brain. In addition, the deep inhalation of cold air during a yawn reduces the temperature of the blood flowing to the brain. Therefore, yawning forces the warmer blood away from the brain and at the same time brings cooler blood from the lungs.

It has been observed that several diseases are associated with a thermoregulation that is considered abnormal, including multiple sclerosis, epilepsy, and migraine[44]. These three clinical conditions present an exacerbation of yawning in moments of crisis or before. In the case of migraine, yawning has been considered the most reliable precursor sign of the headache onset[60].

Thermoregulation and sleep are interrelated homeostatic functions. This interaction occurs at the thermostat level of the preoptic hypothalamic area, such that the onset of sleep initiates a decline in the central body temperature curve. On the other hand, prolonged sleep deprivation in rats caused an increase in the animals' brain temperature[61]. Subjective ratings of sleepiness in humans correlate with increases in skin temperature when individuals are lying down[62] and with increases in core body temperature when standing up. In addition, consumption of warm water causes increases in body temperature and sleepiness[63]. Therefore, the variation in body temperature appears to be related to a corresponding variation in sleepiness.

Another homeostatic function that shares regulatory structures with sleep is the control of eating habits. Orexin is synthesized by the lateral hypothalamus, traditionally known as the "hunger center" and, when released, stimulates the search for food. It can be said that orexin is responsible for the feeling of hunger. In addition to this, orexin is one of the neurotransmitters responsible for the alertness state[64]. The dysfunction of orexin-producing neurons is a marked feature of narcolepsy[15]. Recently, it has been shown that plasma orexin is reduced in migraine patients in the period between seizures, which resulted in the hypothesis that orexin-producing neurons in the hypothalamus are candidates for generating a migraine attack[65].

Other lines of research investigate the role of oxidative stress in the genesis of migraine in which, once again, the association with sleep deprivation turns out be evident.

It's known that trigeminal ganglion neurons, responsible for all painful sensitivity in intracranial structures, express TRPA1 type receptors. More recently it was demonstrated that TRPA1 is activated by oxidative stress and that its activation causes the antidromic release of CGRP, considered a key molecule in neurogenic inflammation and, consequently, in the genesis of migraine pain[66-68]. Several substances that are recognized to cause migraine attacks are capable of activating TRPA1[69].

The review by Borkum[51] indeed evidenced that the most frequent triggers for migraine attacks are capable of generating oxidative stress, which places oxidative stress as a common final pathway in the mechanism of migraine attack genesis. Specially regarding the "sleep deprivation" trigger, it has been demonstrated that sleep deprivation is associated with depletion of an important antioxidant enzyme in the brain: reduced glutathione. It's important to highlight that, in mice, 10% of all gene transcription of this enzyme shows oscillations with the circadian rhythm, suggesting some regulation by clock genes. In particular, the transcription of the main antioxidant enzymes appears to be controlled by these clock genes.

The growing increase of evidence correlating oxidative stress with migraine has led to the emergence of a new perspective on the condition's pathophysiology[70]. Thus, migraine seems be an adaptive response that occurs in genetically predisposed individuals, in whom there is an incompatibility between the brain's energy reserve and the demand of the migraine patient's cortex, hyperexcitable by sensory stimuli. The energy deficit disrupts cortical homeostasis by increasing free radical levels. This increased oxidative stress is sensed by the Panexin family channels, whose opening initiates a cascade of events that culminates in TRPA1 receptor activation, trigeminal-vascular activation, and finally CGRP release. The function of the migraine crisis itself is to restore the cerebral energetic homeostasis by reducing the damage caused by free radicals[71].

Sleep deprivation, by causing oxidative stress in the brain, provokes or aggravates migraine crises. This, in turn, activates TRPA1 receptors located in the 1st order trigeminal neurons, initiating the sensitization process of the trigeminal system which culminates in the release of CGRP in the dural afferents of the trigeminal ganglion neurons. People who suffer from migraine often report an association between insomnia and migraine attacks.

Several studies point to hypothalamic alteration in the pathophysiology of migraine. It's possible that hypothalamic alterations in migraine patients promote sleep alterations. The hypothesis is that there is a hyperactivity of the brain mechanisms responsible for hunger behavior in the premonitory phase of migraine, resulting in excitement and lack of sleep. In this case, "insomnia" would be the very expression of this disorder of the brainstem and hypothalamus nuclei responsible for the sleep-wake cycle. Sleep deprivation imposed by insomnia seems to be capable of generating the migraine crisis through the common mechanism of increased oxidative stress.

CONCLUSION

Sleep deprivation possibly causes or aggravates migraine attacks due to its ability to cause oxidative stress in the brain, which activates TRPA1 receptors located on 1st order trigeminal neurons, initiating the sensitization process of the trigeminal system, which results in the antidromic release of CGRP in the dural afferents of these neurons in the trigeminal ganglion. The association between insomnia and migraine seems to converge to this same pathophysiological process, since sleep deprivation imposed by insomnia would be able to generate the migraine crisis through the increase of oxidative stress.

AUTHORS' CONTRIBUTIONS

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