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Review

The importance of addressing sleep disorders in migraine treatment

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Abstract

Migraine is one of the most common complaints in the clinical practice of neurology. It is multifactorial, with insomnia being a predisposing factor present in almost 50% of cases. The pathophysiology of migraine is complex and involves alterations in several areas of the CNS that share common pathways with sleep disorders. These include hypotha¬lamic connections, hormones, and neuropeptides such as orexin and monoaminergic. Furthermore, there are other specific sleep disorders associated with migraine. Currently, treatment is individualized and lifestyle changes and sleep adjustment are recommended in addition to medication. In view of the above, the association between sleep and migraine represents a therapeutic opportunity that can be exploited based on a detailed clinical approach during clinical examination.

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Introduction

Insomnia is the sleep disorder found in almost 50% of patients diagnosed with migraine.[1] It is also true that there is a higher prevalence of migraine in individuals with insomnia, compared to individuals without this sleep disorder.[2]

While migraine can awaken the patient in the middle of sleep, sleep disruption comply as a trigger for the attack in cases where the pathophysiological mechanisms are shared.[3] Interestingly, a higher occurrence of arousal from migraine attacks can be observed during REM sleep. Some attacks of nocturnal headache occur during dreams, and occasionally the aura of classic migraine attacks is incorporated into the content of a dream preceding awakening with severe headache.[4]

Changes in sleep, such as sleep deprivation, have been identified as triggering factors for single attacks.[5] It is also described that the periodicity of crises follows the circadian cycle, with most seizures occurring in the early morning hours[6], probably related to the activity of monoaminergic neurotransmitters that interfere with REM sleep.[7,8] Also, chronic exposure to insufficient sleep induces changes in pain inhibitory processes, favoring the chronification of the disease.[9]

As soon, by presenting the common pathophysiology, this article purpose to report the complaints of sleep disturbance and migraine, by direct or indirect mechanisms, demonstrating the relevance of addressing the theme on diagnostic routine, as well as in management of the therapy. It also intends to differentiate triggers from prodromes, which often, although associated, have different mechanisms of action and therapeutics.

Sleep and Migraine

Epidemiology

Currently, migraine affects 12 to 15% of the general population.[8,10] It is more common in women between the ages of 30 and 39, with migraine without aura being more prevalent.[11] Migraine, although not fatal, is disabling and ranks 2nd in the ranking that relates illness and years of life lived with disability.[10,12]

On the other hand, in men sleep disturbances related to respiratory alterations and fragmentary myoclonias were more prevalent, while in women insomnia was common.[13,14] The main sexual differences in sleep shows up with the first menstrual cycle.[15] Progesterone looks to decrease the incidences of environment-related sleep disruption by improving the duration and quality of slow-wave sleep.[16] Also, corroborating the relationship between prodromes of migraine and the menstrual cycle are the localization of estrogen and progesterone receptors in the sleep/wake regulatory nuclei, including the basal prosencephalon, hypothalamus, dorsal raphe nucleus, and locus coeruleus.[17]

In addition, workers with journey more than 40 hours per week had a higher prevalence of short sleep duration, while the lowest prevalence was found in the oldest age group (>65 years), followed by the youngest one (18-25 years).[18]

These factors helps to explain the predominance of migraine among females and in productive age people. Moreover, how it is seems that the population has been reducing their sleep time[18,19] this may serve as an alert to clinicians for the increase in the incidence of headache over the years.

Diagnosis

Migraine is a primary headache[20] and its diagnosis is defined by the International Classification of Headache Disorders (ICHD-3). Likewise, sleep disorders can be systematized by the International Classification of Sleep Disorders.[21]

A good anamnesis is essential for the diagnosis of migraine[22], as well as for sleep disorders[23], since they may be related and interfere with the therapeutic strategy and prognosis of the disease. Thus, during the investigation, it is important to ask about the duration and intensity of migraine, prodromes, and possible triggers; questions such as the time of onset and awakening sleep, frequency and duration of awakenings, duration of naps, daytime sleepiness symptoms, fatigue, and sleep environment.[24] Suggesting the patient to keep a sleep diary for a period of two weeks or more, as well as during the headache investigation, contributes to the diagnosis and possibilities correlations. Around the medications, the excess use drugs for acute headache treatment, oral contraceptives, postmenopausal hormone replacement, nasal decongestants, selective serotonin reuptake inhibitors, and proton pump inhibitors can be reported as the trigger the crises.[26]

Migraine Pathophysiology

It has been proposed that migraine would have vascular characteristics, being caused mainly by vasodilation, while aura would arise from vasoconstriction. Nowadays, it is known that it is a complex disorder with genetic, anatomical, physiological and pharmacological components.[27] Also, sleep can be disturbed by musculoskeletal factors or concomitant depression.[28]

Alterations in several areas of the CNS may be linked to prodromal and migraine attacks. For example, the increase in light sensitivity experienced may be secondary to increased activity in the occipital cortex[29]; while brainstem activation can cause nausea.[30] On the other hand, hypothalamic hyperfunction could trigger polyuria, mood and appetite changes and if this occurs in the connecting circuits thalamus to the cortex, the symptom is cutaneous allodynia.[31] The importance of these findings lies in the possibility of defining new therapeutic targets for drugs and neuromodulators, such as transcranial magnetic stimulation.[32]

Anatomical variabilities in the nerve roots may also influence the migraine pattern. Branches of the trigeminal nerve may reach the neck muscles through the skull, suggesting a possible role for these afferents in migraine-related neck pain. Patients with these causes would benefit from local therapies of suboccipital injections of anesthetics and steroids.[33]

Neurotransmitters

To associate sleep disorders and migraine, is fundamental the elucidation of the role of neurotransmitters. Orexins, melatonin, pituitary adenylate cyclase activating polypeptide, serotonin, dopamine, and adenosine are the molecules that represent a possible role as mediators of this relationship.[3] In addition, diencephalic and brainstem anatomical regions are involved in both the pathogenesis of migraine and the regulation of the sleep-wake cycle[9,34] as is shown in Table 1.

Table 1. Anatomical regions and neurotransmitters related to migraine and sleep modulation

Anatomical Region	Migraine	Sleep
Cortex	Pain processing: thalamo-cortical ascending projections synapse on a diffuse network of cortical regions, including the primary and secondary somatosensory motor cortex and visual cortex for pain processing Pain modulation: through direct and indirect descending projections from the cortex to the trigeminocervical complex	Promotion of wakefulness: through ascending inputs from monoaminergic neurons, hypothalamus and basal prosencephalon.
Thalamus	Processing and transmission of nociceptive information from the trigeminocervical complex	Promotion of wakefulness and integration of sub-cortical sleep-wakefulness inputs
Hypothalamus - posterior (dopamine) - lateral (orexin)	Pain processing, transmission, and modulation of the ascending pathway of the brainstem nuclei and trigeminocervical complex The dopaminergic nucleus A11 is responsible for the prodromal symptoms of migraine Orexinergic neurons facilitate or inhibit the trigeminocervical complex by specific receptors and regulate the sleep-wake cycle Orexinergic neurons are also related to the premonitory phase of a migraine attack. It generates symptoms such as yawning, food cravings, and changes in wakefulness.[25]	Promotion of wakefulness, regulation of circadian rhythm and control of sleep-wakefulness transition Promotion of wakefulness by activation of the monoaminergic system of the brainstem, basal prosencephalon, and cortex Sleep-wakefulness transition control- participates in the flip-flop system for sleep-wakefulness transition; maintains the stability of wakefulness; and prevents sudden and inappropriate onset of sleep Significant increases in orexin levels occur after partial sleep deprivation.[35]
Brainstem - Periaqueductal (dopamine) - Dorsal raphe nucleus (serotonin) - Locus coeruleus (norepinephrine)	Transmission of pain by afferent fibers from the trigeminocervical complex to the thalamus Modulation of pain through the descending input of the thalamus and hypothalamus The circadian rhythm of serotonin and the discharge of serotoninergic neurons may influence the production of endogenous opioids and the activity of the trigeminal system.[36] Concentrations of calcitonin gene-related peptide (CGRP) are persistently elevated in patients with chronic migraine, and are released during exacerbation.[37]	Promotion of wakefulness: ascending activation pathways projecting from the brainstem to the thalamus and basal prosencephalon Stabilization of wakefulness: it receives the orexinergic excitatory projections and sends inhibitory inputs to sleep promoting ventrolateral preoptic nucleus to reinforce wakefulness Sleep transition control: inhibition of this nucleus by the ventrolateral preoptic nucleus promotes sleep. Noradrenergic and serotoninergic neurons inhibit REM sleep Increased activity in the trigeminal nuclei during sleep may precipitate a seizure and awaken the patient.[38] Onset of sleep by stimulation of monoaminergic cells in the locus coeruleus.[39]

Adapted from: Tiseo C, Vacca A, Felbush A, et al. **Migraine and sleep disorders: a systematic review**. *J Headache Pain* 2020. 21(1):1-13. The other references are indicated in the table.

Common pathway between the pathophysiology of migraine and sleep disorders

The hypothalamus is involved in the regulation of several physiological processes, such as sleep, circadian cycle, thermal regulation, appetite, cardiovascular and endocrine functions, modulation of the trigeminal nociceptive system, and others. In migraine, many of these functions, as well as their control pathways, are dysfunctional.

In the modulation of pain in migraine, the hypothalamus has a direct action, through connections with the trigeminal-cervical complex; and indirect, through connections with other structures that help in this modulating process, such as the periaqueductal gray matter (PAG) and the locus coeruleus (LC).[40] Migraine results from aberrant activation of the trigeminal-vascular system, promoting alteration of the nociceptive process. Also, there is a hyperactivation of the hypothalamus during the pain crisis[40,41] and prodromal symptoms.[40,42]

Patients with migraine also have alterations in sleep-related neuropeptides, such as orexins. Produced by the lateral hypothalamus, they control the transition between wakefulness and sleep stages. Patients with chronic or episodic migraine present altered levels of these neuropeptides in the cerebrospinal fluid.[40] This may be associated with the reduced REM sleep period found in migraine patients, which in turn is related to more prominent allodynia during attacks.[43] In addition, these neuropeptides act in modulating trigeminal-vascular tone, with orexin A having anti-nociceptive components and orexin B having a pro-nociceptive action.[44] Melatonin also seems to play a role in the association between migraine and sleep disorders, exerting anti-nociceptive effects through the activation of MT2 receptors; but its production, regulated by the hypothalamus, is altered in sleep disorders.[45] Other hormones related to hypothalamic activity, such as cortisol, are also modified.[46]

Triggers and prodromal symptoms related to sleep disorders

In the natural history of migraine disease, two stages precede the pain crisis: exposure to migraine triggers, stimuli believed to precipitate the crisis; and the prodromal stage of the disease, which consists of symptoms that precede the crisis by 2 to 48 hours, occurring before the aura (in migraine with aura) or before the onset of headache (in migraine without aura).[47]

It is estimated that about 75% to 95% of patients report specific triggers for migraine attacks[48] with sleep disturbances among the most important, reported by at least 50% of patients.[1,49-50] Other common triggers are: stress, hormonal changes in women, fasting, bright lights, and odors (such as perfume).[1,9,40,43,45,48,49,51] Patients may have a single trigger or multiple triggers, such as stress and sleep disturbance.[1,48] They may change throughout a lifetime[1] and such characteristics do not seem to vary according to ethnicity or demographic region.[48] Also, the adequate recognition of the migraine attack trigger in each patient plays an important role in the prevention of the disease, through strategies that aim to avoid, as much as possible, the known triggers.[1]

Changes in sleep pattern and other hypothalamic functions are also among the main prodromal symptoms of migraine. Examples are excessive sleepiness, repetitive yawning, mood and appetite variations, fatigue, nausea, and vomiting.[40,47,52] These symptoms appear to be due to hypothalamic hypersensitivity to dopamine.[40,52] This hypothesis was demonstrated experimentally in which the administration of a dopamine agonist increased the incidence of prodromal symptoms in migraine patients[53] and, in another study, in which the administration of domperidone 30g (dopaminergic antagonist), early in the prodromal phase, reduced the incidence of the migraine attack by 61% compared to the placebo group.[54] Other studies have demonstrated, by functional neuroimaging examination, a hyperactivation of the hypothalamus in the prodromal phase.[42] Therefore, the identification of prodromal symptoms offers an important therapeutic window for the prevention of migraine pain attacks.

It is also observed an important correlation between the identified trigger and the prodromal symptom that will be followed.[55] Some examples are shown in Table 2. Thus, some authors suggest the possibility that some triggers may be early manifestations of the prodromal phase of the disease.[55,52]

Table 2. Relationship between trigger perception and the corresponding prodromal symptom.

Reported trigger	Prodromal symptom
Light Stimuli	Photophobia
Sound stimuli	Phonophobia
Skipping meals	Food cravings
Stress	Mood swings, neck stiffness
Dehydration	Excessive thirst
Poor sleep	Fatigue, drowsiness

Adapted from: Karsan N, et al. **Are some patient-perceived migraine triggers simply early manifestations of the attack?**. *J Neurol* 2021. 268(5):1885-1893. DOI:10.1007/s00415-020-10344-1

Sleep disorders, besides serving as triggers, negatively influence migraine in several ways: poor sleep quality is considerably more frequent in adults with migraine; it increases the frequency and intensity of attacks, as well as favoring the chronification of the disease, regardless of the presence of psychiatric comorbidities, such as depression and anxiety.[9,43,56,57]

Migraine and specific sleep disorders

Migraine and sleep disorders are often associated comorbidities and, individually, very prevalent. It is known that patients with inadequate sleep routine present cognitive impairment, short attention span, irritability, daytime sleepiness, mood swings, stress, and even increased appetite and hunger perception.[58-61] These symptoms are present both in acute sleep deprivation and in chronic impairment of its quality or duration.[59] It is worth noting the intersection between these symptoms and those present in migraine, as shown in Table 3.

Table 3. symptoms related to sleep pattern changes compared to prodromal symptoms of migraine

Symptom of insufficient sleep	Prodromic Symptom of Migraine
Mood swings, irritability	Mood swings
Increased perception of hunger	Food cravings
Daytime sleepiness, reduced attention span	Fatigue, drowsiness

However, the mechanisms by which each sleep disorder influences the onset and development and evolution of migraine are still unknown. In Table 4, the main categories of these disorders and their possible correlations with migraine are compiled, according to the ICSD.[21]

Table 4. The major categories of sleep disorders and correlations with migraine.

Sleep disturbance category	Correlations with migraine
Insomnia	Studies suggest a bidirectional relationship between migraine and insomnia, in which insomnia is a risk factor and promotes worsening of the clinical presentation and course of migraine with increased pain intensity, frequency of attacks, and chronicity of the disease; individuals with migraine have a higher risk of developing insomnia .[9]
Sleep-Related Respiratory Disorders	
Obstructive sleep apnea (OSA)	Although there is no clear association between the two comorbidities [9,41], some evidence suggests that obstructive sleep apnea may play a trigger role in migraine in predisposed patients and may promote exacerbation of headache frequency and severity.[9]
Sleep-Related Movement Disorders	
Restless legs syndrome (RLS)	The presence of RLS in patients with migraine is associated with greater severity of the disease, with increased frequency of attacks, occurrence of photophobia, phonophobia, nausea, and higher anxiety and depression scores than in individuals without RLS. It is theorized that the association between migraine and RLS is due to a dopaminergic dysfunction in the hypothalamic nucleus A11.[9,62] The presence of RLS is more common in patients with the chronic form of migraine than with the episodic form.[45]
Central hypersomnia disorders	
Narcolepsy	Patients with narcolepsy have a higher prevalence of migraine.[9] Although the association between both comorbidities is controversial, narcolepsy stems from a dysfunction of the orexinergic system, which also appears to be related to migraine.[9]
Circadian rhythm disorders	Some studies have reported an association between migraine and the circadian cycle.[9,45,44] Migraine attacks occur more frequently in the morning and those that occur in this period are more severe.[45] There is no clear association between both comorbidities.[9]
Parasomnias	
Sleepwalking	Adults with migraine appear to have a higher prevalence of sleepwalking in childhood[45] and adults with sleepwalking have a higher risk of developing migraine or any other headache, regardless of associated comorbidities such as depression, chronic insomnia, and daytime sleepiness.[9] Possibly stems from alterations in the serotonergic and orexinergic pathways.[46]
REM sleep behavior disorder	The presence of dream staging was associated with greater migraine-related disability and poorer sleep quality.[9,63] More studies should be done to evaluate the possible correlation between behavioral REM sleep disorder and migraine.[9,45]

Conclusion

Migraine and sleep disorders are common clinical conditions in the general population, often associated with other diseases. This fact is likely due to overlapping modulatory mechanisms. Thus, for the treatment of migraine, it is essential the analysis of triggers during anamnesis and management through lifestyle changes, such as: regularizing sleep patterns, weight loss and increased physical exercises; avoidance of alcohol and caffeine consumption; control of comorbidities (such as hypertension, psychiatric, endocrine, and others).

Although current preventive therapies are effective for mild cases, there is a significant need for safer treatments.[64] Triptans, nonsteroidal anti-inflammatory drugs, and antiemetics remain mainstays in acute migraine therapy. However, in view of the recognition of the neurotransmitters involved in the crises, drugs that interfere in these pathways may be effective in the treatment. Drugs with action on neurotransmitters common to sleep disorders and migraine, such as CGRP antagonists and modulators of central monoaminergic pathways and orexins, may also be effective.[65-67] Also, migraine attacks with different clinical features may respond differently, and the management of specific exacerbating factors and the personalization of acute and preventive therapeutic approaches should be considered.[26] Therefore, in this article, we emphasize the importance of looking for disturbances and changes in sleep patterns during the clinical examination of migraine patients, especially when headache is difficult to control.

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