



## Obstructive sleep apnea and headache: an integrative review of the last 18 years

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### Abstract

#### Introduction

Obstructive sleep apnea (OSA) is a prevalent and underdiagnosed clinical condition, characterized by the presence of repetitive airway collapse during sleep, resulting in oxyhemoglobin desaturation and sleep fragmentation. Among the most frequent reports of patients with OSA, is morning headache or chronic daily headache, which in 2004 received its own classification in the International Classification of Headache Disorders (ICHD-2) as sleep apnea headache.

#### Objective

The present review aims to evaluate the available scientific literature on the association between OSA and headache after classification, totaling a period of 18 years.

#### Results

In 8 included studies, 1,637 patients were analyzed, observing a bilateral and frequent association between the two pathologies.

#### Conclusion

However, there is still no consensus on the mechanism behind this relationship, and the results of studies are divergent.



## Introduction

Obstructive sleep apnea (OSA) is a clinical condition characterized by the presence of repetitive airway collapse during the sleep period, resulting in oxyhemoglobin desaturation and sleep fragmentation, associated with resulting symptoms such as daytime sleepiness.<sup>1,2</sup> In the adult population, its average incidence is 14% in men and 5% in women, however, only 1 in 50 patients with the syndrome is diagnosed and treated.<sup>1</sup>

Due to this underdiagnosis, the American Academy of Sleep Medicine recommends assessing sleep quality and nocturnal sleepiness as a routine for health maintenance in adults.<sup>3</sup> Among the validated OSA screening instruments, the Berlin Questionnaire and the STOP-BANG questionnaire are the most used in clinical practice, both having sensitivity and about 85%, still requiring diagnostic confirmation by Polysomnography (PSG).<sup>4</sup>

The pathophysiological mechanism of OSA is complex and multifactorial. Apneas and hypopneas can occur in the context of decreased upper airway caliber due to obesity or maxillofacial or pharyngeal abnormalities.<sup>5</sup> In addition, other factors, such as pharyngeal neuropathy, may impair the protection of upper airway reflexes or the displacement of rostral fluid from the legs to the neck during sleep, contributing to obstruction.<sup>6</sup>

Among the most frequent reports of patients with OSA, there is morning headache or chronic daily headache.<sup>7,8</sup> The proposed mechanism occurs as a consequence of repetition apneas, which causes hypoxemia due to decreased blood oxygen saturation and consequent cerebral vasodilation due to increased carbon dioxide partial pressure, but also due to sleep fragmentation.<sup>9,10</sup>

The diagnostic criteria for sleep apnea headache were established in 2004 in the second edition of the International Classification of Headache Disorders. According to this classification, the diagnosis is made when the patient has headache on waking up to 30 minutes, bilateral, not accompanied by nausea, on more than 15 days a month, in addition to OSA diagnosed by PSG. In addition, headache ceases with OSA treatment.<sup>11</sup> However, despite the prevalence and recognition as an individual classification of headache, there is still no consensus on the relationship between sleep apnea and headache. Therefore, the present review aims to study the association between headache and OSA through the last 18 years of published scientific literature.

## Methods

This is an integrative review of the available scientific literature on the presence of headache in patients diagnosed with OSA in the last 18 years. For this, the PubMed, Web of Science and Google Scholar online databases were accessed, using the descriptors "Obstructive Sleep Apnea" and "Headache".

Original articles published from the sleep apnea headache classification (2004) in which the relationship between OSA and headache is in evidence were included in the review. Editorials, comments, letters to the editor, literature reviews and other articles that were not fully available or did not have accurate information were excluded.

## Results

After applying the inclusion and exclusion criteria, 8 studies were included, totaling 1,637 patients analyzed in this review. All studies were observational and retrospective, differing in their approach in: (a) studies that assessed the presence of morning headache in patients diagnosed or with a high probability of having OSA and (b) studies that assessed the presence of OSA in patients with headache. Tables 1 and 2 summarize the included studies according to the aforementioned profile.

**Table 1.** Studies that assessed the presence of headache in patients with morning headache

| Study                            | OSA patients |       | non-OSA patients |      |
|----------------------------------|--------------|-------|------------------|------|
|                                  | n            | %     | n                | %    |
| KoC et al. <sup>12</sup>         | 361          | 38.5  | 107              | 35.5 |
| Kristiansen et al. <sup>13</sup> | 296          | 11.8  | 237              | 4.6  |
| Alberti et al. <sup>14</sup>     | 55           | 34.54 | 50               | 20   |

**Table 2.** Studies that assessed the presence of OSAS in patients with headache

| Study                              | Total sample | Headache type    | OSA patients  |
|------------------------------------|--------------|------------------|---|
| Spalka et al. <sup>15</sup>        | 328          | Morning headache | OSA parameters in PSG were decreased in patients with morning headache (p<0.01) |
| Chen et al. <sup>16</sup>          | 63           | Morning headache | 50 (79.36%)   |
| Mitsikostas et al. <sup>17</sup>   | 72           | Chronic headache | 21 (29.16%)   |
| Nobre et al. <sup>18</sup>         | 37           | Cluster headache | 21 (58.3%)  |
| Graff-Radford et al. <sup>19</sup> | 31           | Cluster headache | 25 (80.64%)   |



## Discussion

Headache and sleep disorders are common in the general population and their association has been studied for over a century.<sup>9</sup> In the symptomatology of OSA, episodes of headache upon waking are frequent, often referred to as Morning Headache (MH).<sup>7,8</sup> This nomenclature, however, is controversial and used to classify headaches of different etiologies. It is estimated that 7.6% of the population has MH, in addition to other clinical conditions reporting high levels of its occurrence, such as depression, insomnia and restless legs syndrome.<sup>16</sup>

Sleep apnea headache (SAH) was primarily classified in 2004 according to the International Classification of Headache Disorders (ICHD-2), as a MH of tension characteristics.<sup>11</sup> In 2013, however, an update to the ICHD was published, bringing some changes in the classification of this type of headache.<sup>20</sup> Table 3 compares the diagnostic criteria of the two classifications.

**Table 3.** Comparison of diagnostic criteria for sleep apnea headache between ICHD-2 (2004) and ICHD-3 (2013)

| ICHD-2  | ICHD-3  |
|---|---|
| <p>A. Recurrent headache with at least one of the following characteristics, and fulfilling criteria C and D:<br/>                     A1. Occurs on &gt;15 days per month<br/>                     A2. Bilateral, pressing quality and not accompanied by nausea, photophobia or phonophobia<br/>                     A3. Each headache resolves within 30 minutes<br/>                     At least one of the A1–A3 criteria</p> <p>B. Sleep apnea (Respiratory Disturbance Index &gt; 5) demonstrated by overnight polysomnography</p> <p>C. Headache is present upon awakening</p> | <p>A. Headache present on awakening after sleep and fulfilling criterion C</p> <p>B. Sleep apnea (apnea-hypopnoea index &gt; 5) has been diagnosed</p> <p>C. Evidence of causation demonstrated by at least two of the following:<br/>                     1. headache has developed in temporal relation to the onset of sleep apnea<br/>                     2. either or both of the following:<br/>                     a) headache has worsened in parallel with worsening of sleep apnea<br/>                     b) headache has significantly improved or remitted in parallel with improvement in or resolution of sleep apnea<br/>                     3. headache has at least one of the following three characteristics:<br/>                     a) recurs on &gt;15 days per month<br/>                     b) all of the following:<br/>                     (i) bilateral location<br/>                     (ii) pressing quality<br/>                     (iii) not accompanied by nausea, photophobia or phonophobia<br/>                     c) resolves within 4 hours</p> |
| <p>D. Headache ceases within 72 hours, and does not recur after effective treatment of sleep apnea</p>  | <p>D. Not better accounted for by another ICHD-3 diagnosis.</p>   |

Despite the established criteria, most studies that assessed headache in patients with OSA used a broader definition of MH. A Norwegian study, however, differentiated SAH from other causes of MH through PSG. The OSA group presented a prevalence of 11.8% of SAH while the control group presented a prevalence of 4.6% of MH. In addition,

the clinical characteristics of both headaches were accessed, with no significant differences between the groups. Pain characteristics were predominantly reported as pressure/squeezing, of mild or moderate intensity and of bilateral location in both groups. There were few accompanying symptoms reported. Most patients reported that their morning headache lasted more than 30 minutes.<sup>13</sup>

In another study, Alberti et al.<sup>14</sup> observed an increased prevalence of MH in individuals with OSA compared to individuals with insomnia, another etiology of MH. In relation to patients with OSA, SpO2 values after apnea episodes were found to be reduced among patients who reported MH (82.5% vs. 86.1%,  $p < 0.03$ ). In contrast, Koç et al.<sup>12</sup> did not observe a significant difference in the presence of MH between individuals with OSA and control individuals (38.5% vs. 35.5%,  $p = 0.575$ ). When comparing individuals with OSA with and without MH, significant increases were found in the proportion of females ( $p = 0.001$ ), Epworth sleepiness scale score ( $p = 0.002$ ) and daytime sleepiness ( $p = 0.002$ ) in the MH group. Indicating a possible relationship between the female hormonal axis and the severity of OSA with the presence of headache.

In an opposite approach to the aforementioned studies, Chen et al.<sup>16</sup> analyzed the presence of OSA in patients with MH. Among the 63 patients who reported MH in the clinical interview, 50 (79.36%) were diagnosed with OSA after PSG. Furthermore, 35 (55.55%) of these patients were diagnosed with migraine during the study, indicating an overlap of the two pathologies. Following the same approach, Spatka et al.<sup>15</sup> studied polysomnographic data from patients who reported MH. In contrast to previous studies, the apnea and apnea-hypopnea indexes were observed to be reduced in patients with MH in relation to the control group ( $p = 0.01$ ). This result casts doubt on the proposed mechanism for SAH, requiring further polysomnographic studies in this population.

Two other types of headache, cluster headache (CIH) and chronic headache (ChH) were also associated with the presence of OSA in the literature. CIH is characterized by extremely severe headache, ipsilateral, with orbital, supraorbital and/or temporal location with associated autonomic features, such as tearing, conjunctival hyperemia, rhinorrhea, congestion, hyperhidrosis and eyelid edema, usually on the side ipsilateral to the pain.<sup>21</sup> Nobre et al.<sup>18</sup> found increased apnea-hypopnea index levels in patients with CIH undergoing PSG ( $p < 0.001$ ). Stratified analysis in relation to BMI and age determined



an 8.8-fold increased chance in patients with CIH to have OSA, increasing to 26-fold in patients with a BMI above 25. Graff-Radford et al.<sup>19</sup> also found a high prevalence of OSA in patients with CIH (80.64%). In addition, an average drop in SpO<sub>2</sub> to 88.4% was observed, configuring an intermediate desaturation.

Only one study evaluated the presence of OSA in patients with ChH. Mitsikostas et al.<sup>17</sup> analyzed 72 individuals with CC, in which 21 (29.16%) were diagnosed with OSA. After starting CPAP treatment, 5 (23.8%) of these patients reported a decrease in headache frequency. However, 14 (66.6%) had an increase in the frequency of attacks, requiring specific drug treatment for the headache.

## Conclusion

The association between headache, regardless of classification, and obstructive sleep apnea was present in all the analyzed literature, differing in the possible pathophysiological mechanism. The analyzed studies showed discordant results regarding changes in apnea and desaturation parameters obtained in the polysomnography of headache patients, and further studies on this association are necessary.

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