Cluster Headache and Obstructive Sleep Apnea: Are They Related Disorders?

Steven B. Graff-Radford, DDS, and Antonia Teruel, DDS, MS, PhD

Corresponding author
Steven B. Graff-Radford, DDS
The Pain Center, Cedars-Sinai Medical Center, 444 South San Vicente, #1101, Los Angeles, CA 90048, USA.
E-mail: graffs@cshs.org

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Patients with cluster headache (CH) have a higher prevalence of sleep apnea, and a possible relationship between these two conditions has been proposed. Although patients suffering from CH attacks often wake up from sleep, sleep apnea has been suggested to be a trigger or an associated abnormality in CH. It has been proposed that regulation of the hypothalamus may be responsible for sleep apnea, and that similiarly CH is generated in the hypothalamus. However, there is evidence that CH and obstructive sleep apnea are not causal, but rather parallel processes both generated in the hypothalamus. The exact role that sleep apnea plays in the perpetuation or precipitation of CH is still to be determined. This paper discusses the proposed pathophysiological mechanisms of these two entities and the possible relationship between CH and sleep apnea.

Introduction

According to the International Headache Society's Classification of Headache Disorders, cluster headache (CH) is defined as "attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15–180 minutes and occurring from once every other day to 8 times a day" [1]. The attacks are accompanied by at least one of the following ipsilateral autonomic signs: conjunctival injection, lacrimation, nasal congestion, forehead and facial sweating, miosis, ptosis, and/or eyelid edema. Another distinct characteristic is that patients are restless or agitated during the CH attack [1]. As it is implied by the name of this condition, these headaches occur in clusters lasting weeks to months, and between the cluster episodes the patient is pain-free. Moreover, CH is also characterized by its nocturnal periodicity. The nocturnal attacks may make up 50% to 60% of the attacks [2]. Characteristically, CH is associated with the rapid eye movement (REM) period of sleep and may sometimes occur during or at the end of this period [3,4]. In about 50% of the cases, patients wake up with a headache within 2 hours of falling asleep [1,5]. In patients with the episodic form of CH (ECH), the nocturnal attacks have been described to occur during REM sleep about 50% of the time [4,6]. The prevalence of CH has been reported to be approximately 53 cases per 100,000 people per year [7•]. Men are affected more commonly than women in a proportion ranging from 2.5:1 to 7.1:1 [7•,8]. CHs are treated preventively with calcium channel blockers [9,10], steroids [11], or antiepileptic medications [12]. For abortive treatment of acute attacks, oxygen along with triptans or ergotamine as well as steroids are treatments of choice [13•].

Sleep apnea is defined as a repeated, brief interruption in breathing that occurs during sleep and is usually associated with reduction in blood oxygen. Sleep apnea has been classified into two types: central and obstructive [14]. In central sleep apnea, there is reduction or even lack of output from the hypothalamus (the part of the brain responsible for breathing); therefore, no signal is sent to the breathing muscles, resulting in apneic episodes. On the other hand, in obstructive sleep apnea (OSA), there is a physical obstruction of the upper airway. In both cases there is a reduction in blood oxygen saturation, which is considered mild when the blood saturation is 85% to 89%, moderate when 80% to 84%, and severe when less than 80%. During an apneic episode, as the blood levels of oxygen decrease and the levels of carbon dioxide increase, the brain is alerted and sends signals to muscles responsible for breathing to function, causing an "arousal" that results in the termination of the apneic event. Consequently, sleep is interrupted by the arousals, preventing the patient with sleep apnea from getting restorative sleep and ultimately resulting in excessive daytime sleepiness

and fatigue. Sleep apnea tends to occur more in men than women and has a higher prevalence in overweight and hypertensive patients [15–17]. However, it can occur in all age groups [18]. Sleep apnea is treated with continuous positive airway pressure (CPAP) [19,20•], dental devices (eg, the UCLA modified Herbst device, Thornton Adjustable Positioner [Airway Management, Inc., Dallas, TX], SomnoMed Mandibular Advancement Splint [SomnoMed, Crows Nest, NSW, Australia]) [20•,21,22], weight loss [23], and surgery [24•,25].

A relationship between sleep apnea and CH has been proposed, and an increased prevalence of sleep apnea in patients with CH has been found. Furthermore, sleep apnea has been suggested to be a trigger or an associated abnormality in CH. This paper discusses the proposed pathophysiological mechanisms of these two entities and the possible relationship between CH and sleep apnea.

Discussion

Several studies have described that patients with CH also present with sleep apnea. The first study was done by Kudrow et al. [2] in 1984. In their study, six of 10 patients with CH who were studied presented with sleep apnea. Chervin et al. [26] recruited patients with CH and reported that 80% of them had an Apnea/Hypopnea Index of more than 5. Similar figures were found in a study done by Graff-Radford and Newman [27], in which 80.64% of the 31 patients diagnosed with ECH also suffered from sleep apnea. More recently, Nobre et al. [28] reported a higher prevalence of sleep apnea in patients with CH when compared with the control group (58.3% vs 14.3%, respectively). Furthermore, it has been proposed that the oxygen desaturation during an apnea event may be one of the triggers for CH. Two facts support this hypothesis: 1) oxygen administration is efficient in aborting CH attacks and 2) provoked hypoxic states trigger CHs [29–32]. Furthermore, few case reports show that treating the apnea with CPAP may prevent the development of CHs [33,34]. These reports further support the idea that CH may be triggered by the decrease in blood oxygen saturation from sleep-disordered breathing (SDB), particularly in patients whose CHs happen at night. However, Nobre et al. [28] reported a lower association, with only 31.3% (5 of 16) of the patients with ECH having apnea. In their study, they reported that only two of those patients who suffered from both conditions (ie, sleep apnea and cluster) and were treated with CPAP resolved their apnea as well as the headache. The author (Graff-Radford) has treated many patients with dental devices and confirmed successful control of the apnea with polysomnographic study, yet with no benefit to the cluster.

Rhythmicity is a characteristic feature of CH. The attacks tend to recur at the same time of the year and the day for the same patient. It has been reported that 66% to 75% of CH attacks occur at night, during sleep [35,36]. These characteristics suggest a dysfunction in the hypothalamus, the main regulator of circadian cycle, as the cause of CH. In fact, the role of the hypothalamus in CH has been confirmed. Studies using positron emission tomography were performed in patients that had CHs triggered experimentally with nitroglycerin. These imaging studies showed that during an acute attack, CH patients had increased regional blood flow in the hypothalamus that was ipsilateral to the side of pain, as compared with control patients who were cluster sufferers but were not in an active pain state [37,38]. Interestingly, similar activation of the ipsilateral inferior hypothalamus was observed in patients while they were having a spontaneous CH attack [39]. A dysfunction of the hypothalamus may be responsible for impaired carotid body activity and for triggering secondary autonomic system involvement. Additionally, central inhibition of the sympathetic vasomotor tone and parasympathetic stimulation may result from impaired activity of chemoreceptors [40].

Dysregulation in the hypothalamic-pituitary-adrenal axis has been implicated as one of the conditions associated with OSA, suggesting that the hypothalamus could be involved, at least partly, in the pathophysiology of OSA [41,42]. Regulation of sleep occurs in the hypothalamus. Specifically, it has been established that the anterior hypothalamus is the structure responsible for promoting sleep [43]. Moreover, neurons found in the specific regions of the hypothalamus (eg, the preoptic area) are sensitive to temperature and play a role in controlling sleep. McGinty et al. [44] investigated the effects of heating the preoptic/anterior hypothalamus (POAH) in cats. Their results demonstrated that by activating the temperature-sensitive neurons in the POAH, there is a suppression of the airway dilator muscles and the diaphragmatic muscle activity during nonrapid eye movement sleep (NREM). It has been suggested that this loss of muscle tone may lead to SDB. In this paper, the authors suggested that there may be a coupling between metabolic control (which is mediated by the hypothalamus) and airway regulation. Moreover, they suggested that there may be a relationship between metabolic rate (which is controlled by POAH), weight gain in early adulthood, and OSA. Increased activation of the POAH temperature-sensitive neurons could result in a low metabolic rate, consequently leading to weight gain and reduced airway dilator muscle activity. OSA can arise from the combination of these factors [44].

Conclusions

Oxygen desaturation may be the trigger for CH, a hypothesis supported by the fact that oxygen can abort a CH [31]. It has also been proposed that the regulation of the hypothalamus may be responsible for sleep apnea, and that similiarly CH is generated in the hypothalamus. Even

though there is evidence that CH and sleep apnea have both their pathophysiology related to the hypothalamus function, the findings of May et al. [37] and McGinty et al. [44] lead us to believe that CH and OSA are not causal, but are parallel processes generated in the different areas of the hypothalamus. The fact that treating sleep apnea does not necessarily prevent CH attacks further corroborates our hypotheses. Despite some reports that OSA therapy helps the CH, it is the authors' experience that patients with cluster in whom the OSA is controlled still have CH episodes. CH may arise from physiologic activation combined with triggers, such as respiratory muscle during REM sleep as well as bradycardia and hypoventilation in NREM sleep. Altitude, sleep apnea, and vasodilator agents may also be contributing factors.

Disclosures

Dr. Steven B. Graff-Radford is on the speakers' bureau of and works as a consultant for Allergan, Inc., GlaxoSmith-Kline, Merck, Inc., Ortho-McNeil, and Pfizer, Inc.

No other potential conflicts of interest relevant to this article were reported.

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