Topical Review: Cluster Headache and Sleep-Related Breathing Disorders

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This article reviews the existing literature of the common anatomic and physiologic aspects of cluster headache and sleep-related breathing disorders to point out evidence suggesting potential therapies beneficial for both maladies. A search of PubMed, as well as relevant textbooks, was conducted using the terms cluster, headache, sleep, apnea, pain, and chronobiology to find any previously published work that may connect the two disorders. Relevant references in the literature were also investigated. As a group, cluster headache patients tend to have a higher incidence of sleep-related breathing disorders as compared to the noncluster headache population. While commonalities in anatomy and physiology exist, robust evidence linking the two disorders is currently lacking. Many people are unaware that they suffer with a sleep-related breathing disorder. The high incidence of these two disorders occurring together should prompt the clinician who treats cluster headache patients to be acutely aware that a yet undiagnosed sleep disorder may also be present. J OROFAC PAIN 2011;25:291–297

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Headache and sleep disorders tend to be the most common complaints encountered in clinical health care practices.[1] Indeed, the relation between headaches and sleep has been known for some time.[2] Migraine, cluster headache (CH), and hypnic headache (HH) all appear related to sleep stages, which could be suggestive of a chronobiologic pain disorder.[3] CH, reportedly the most painful of the primary headache disorders, is a rare syndrome and displays unique clinical features.[4] The attacks have been reported to occur during nocturnal sleep, either exclusively or very frequently in 50% to 60% of CH patients.[5–8] In most instances, the attacks occur during or around the time of rapid eye movement (REM) sleep.[9] CH is reported to be associated with a state of hyperactivation of the posterior hypothalamus.[10–12] The posterior hypothalamus also plays a critical role in the inhibitory control of the mechanisms of REM sleep.[13,14]

It is reported that approximately 50% to 80% of a heterogeneous pain population has a self-report of some type of sleep disturbance.[15,16] Many of these patients will not necessarily report excessive daytime sleepiness.[17] Approximately 20% to 25% of men are affected by obstructive sleep apnea (OSA) or upper-airway resistance syndrome (UARS).[18] Sleep-related breathing disorders (SRBDs) tend to present on a continuum from UARS to snoring to partial obstruction lasting at least 10 seconds (hypopnea), to complete obstruction and cessation of airflow lasting at least 10 seconds (apnea).[19,20] OSA is presently considered the second most common sleep disorder and is the most severe of the spectrum of SRBDs, affecting 3% to 7% of

adults.[21] Hypoxia has been suggested as a potential factor for the triggering of attacks during cluster periods.[22–24] SRBDs tend to be worse during REM sleep, which could potentially explain why CH is often linked with this stage of sleep.[1] Several case reports have demonstrated a positive outcome in CH patients when their SRBD was treated successfully.[25–28] This further suggests a correlation between these two disorders; however, studies such as those conducted by Nobre et al[29] demonstrated a different outcome.

The purpose of this article was to review commonalities in the anatomical and pathophysiological aspects of these disorders and the potential for a similar etiology. A search of PubMed as well as relevant textbooks was conducted using the terms cluster, headache, sleep, apnea, pain, and chronobiology to find any previously published work that may connect the two disorders. Relevant references in the literature were also investigated.

Anatomic and Physiologic Aspects of Sleep

Sleep and pain are similar in that they are both highly regulated, complex, and multifactorial processes involving multiple structures of the central and peripheral nervous systems. At the core of both entities is the midbrain.[30] In the discussion of sleep anatomy, it is first necessary to delineate the structures responsible for arousal and those involved in initiating and maintaining the sleep states. Arousal mediators are primarily cholinergic and monoaminergic nuclei that interact with the thalamus and hypothalamus.[31] Two different arousal streams have been identified that appear to act separately yet in concert with one another.[32] The first stream arises from the pedunculopontine nucleus and the lateral tegmentum and acts to suppress sleep-promoting activity in the thalamus.[32] The second stream is a more diffuse projection from the basal forebrain and brainstem to the hypothalamus.[32] These excitatory projections have an effect on orexin which is important in both sleep induction and pain processing.[33] Sleep is primarily regulated by a circadian mechanism originating in the suprachiasmatic nucleus (SCN) of the hypothalamus.[34] This intrinsic mechanism is not dependent on physical activity. It is entrained by the light-dark cycle via retinal input and melatonin production from the pineal gland during the dark hours.[34] Interestingly, the SCN also communicates with autonomic structures of the hypothalamus, controlling processes such as corticosteroid homeostasis and thermoregulation, both important mechanisms in the sleep-wake homeostasis.[35]

Anatomic and Physiologic Aspects of Headache

Sensory innervation of the head and face involves primarily the fifth cranial or trigeminal nerve (TN).[36] The specific portion of the TN involved in the pain associated with headache is the ophthalmic or first division.[37] The A-delta and C-fiber afferent of the ophthalmic division bring information from the intracranial vessels and the meninges to the trigeminal brainstem sensory nuclei including subnucleus caudalis (TNC).[37] However, sensation from the cranial posterior fossa may also be mediated by cranial nerve 10 (CNX) and fibers from the dorsal root ganglion of C1-C3.[38]

It is well known that pain and sleep are very closely related to mood and autonomic function.[39,40] This suggests that autonomic homeostasis has a significant influence on the overall pain experience.[41] Another integral part of the pain-modulating mechanism is the descending pain-control system. The human descending pain-control system consists of four tiers: the cortical and diencephalic systems, the mesencephalic periaqueductal grey (PAG) sites, the rostroventral medulla (RVM), in particular its nucleus raphe magnus (NRM), and the spinal dorsal horn and medullary dorsal horn (ie, TNC).[42] Early studies by Mayer et al suggested that stimulation of the PAG would selectively modulate neuronal responses to noxious stimuli but leave intact responses to non-noxious and tactile stimulation.[43] This view of preferential modulation has also been expressed by others.[44,45] Other studies involving stimulation of the PAG or NRM, however, have demonstrated a nonselective inhibition of both nonnociceptive and nociceptive neuronal responses in the dorsal horn.[46–49] Furthermore, while the inhibitory system is involved in the opiate-related mechanisms of pain control, it has also been described in other non-nociceptive functions such as sleep.[50] This would suggest that raphe-initiated effects are not specific to inhibition of nociception, and is further indicated by findings that the PAG and NRM exert depressive effects also on trigeminal and spinothalamic non-nociceptive neurons as well.[51–54] Sessle et al demonstrated that the descending influences are also of importance in the regulation of respiration and buccopharyngeal reflexes.[55]

There is also evidence that the descending control can be facilitory as well as inhibitory.[56] Review of the processes within the RVM suggests that the mechanisms for the bidirectional control of this system are based on two groups of neurons known as ON-cells and OFF-cells.[57] These cell clusters are selectively recruited by higher brain centers important

in psychological stress, illness, and fright, to either inhibit or accentuate painful conditions.[45] Several authors have demonstrated that, in some rat models, noradrenergic neurons in the locus coeruleus (LC) innervate the dorsal horn and provide modulation of nociceptive signaling.[58–62] The LC and raphe nuclear complex (ie, PAG-RVM) are also involved in arousal and can produce inhibition of REM sleep.[63]

The PAG-RVM complex is especially interesting in regard to sleep and headache. Activity in this area has been said to produce behaviors similar to those seen in migraine headache.[64] It has been demonstrated that the PAG may play a role in modulating trigeminovascular inputs.[65] Also, the PAG-RVM complex is a REM-off region when stimulated by orexin.[66] Orexin (type A) inhibits dural vasodilatation, thereby inhibiting the release of calcitonin gene-related peptide (CGRP) in trigeminal neurons.[67] Orexin A injected into the posterior hypothalamus decreases A-delta and C-fiber activation to dural electrical stimulation as well as responses to noxious thermal stimulation of the skin of the face.[68]

The Role of Melatonin

Melatonin is produced in the pineal gland and is synthesized from serotonin.[69] Information from the SCN controls the nightly production of melatonin in a highly regulated manner.[69] In addition to its role in maintaining homeostasis of the sleep-wake cycle, melatonin is also involved in seasonal behavioral changes based on the light-dark cycle.[70] Melatonin increases the inhibitory action of gamma-aminobutyric acid (GABA).[71] Therefore, a decrease in production of melatonin could potentially result in a lowered nociceptive activation threshold normally modulated by GABA.[72] CH patients have demonstrated a decrease in both peak and normal melatonin levels.[73] During the cluster periods, the melatonin levels are even more significantly reduced.[74] Thus, based on its chronobiologic nature, alterations of melatonin secretion in CH patients are suggestive of a putative relationship.[75] Treatment with melatonin in CH has been shown to reduce the frequency of attacks in episodic but not chronic CH patients.[76,77]

Hypoxia has been demonstrated to reduce secretion of melatonin in some individuals.[78] Melatonin also acts as a potent antioxidant and free radical scavenger, suggestive of a potential protective role for melatonin in hypoxia if it is functioning normally.[79]

CH and SRBDs

Although CH is considered rare in comparison to migraine headache, it is a primary headache disorder with a prevalence of 53 cases per 100,000 people per year.[80] It affects men more than women at a rate of 2.5:1 to 7.1:1.[80,81] The diagnostic criteria for CH include at least five "attacks of severe, strictly unilateral pain in orbital, supraorbital, or temporal regions or in any combination of these sites, lasting 15 to 180 minutes and occurring from once every other day to eight times a day."[82] Parasympathetic hyperactivity can be manifested in ipsilateral tearing of the eye, conjunctival injection, and rhinitis.[83] Also, the ipsilateral side of the face may appear red and diaphoretic.[83] Sympathetic hypoactivity is evidenced by the combination of ipsilateral ptosis and miosis during attacks.[84] The combination of ptosis and miosis on one side is referred to as Claude Bernard-Horner syndrome.[85] A sense of restlessness is also characteristic of CH and may aid in the diagnosis if other signs are absent.[82] CH rarely presents in childhood or adolescence, but it tends to become more prevalent in the second decade and usually declines in the fifth decade.[86] The pattern of the pain of CH will typically present at specific times of the day or during sleep.[63]

CH, migraine, and other headaches have been shown to be associated with arousal from and disruptions of REM sleep.[9,87] In 1970, Dexter and Weitzman reported on the first polysomnographic study of chronic migraine and CH.[88] Their findings indicated that CH attacks occurred during REM sleep or within 9 minutes of the end of the REM period. This led to the view that CH was a REM sleep-related disorder.[89] Bono et al demonstrated that sleep deprivation can curtail attacks in some CH patients.[90] A similar outcome was observed in patients who took REM-delaying medications such as benzodiazepines.[90]

SRBDs are associated with recurrent nocturnal hypoxemia, hypercapnia, increased negative intrathoracic pressures, increased intracranial pressures, and other physiologic changes, any of which could potentially act as a triggering mechanism for CH.[91] Most patients with OSA remain undiagnosed, even when presenting symptoms and signs of excessive daytime sleepiness.[18] It is suggested that OSA is due to anatomic airway narrowing and alterations in upper airway neuromuscular tone during sleep.[92] CH has been reported to occur in 31% to 80% of CH patients.[93,94] CH patients have an eight times higher risk of exhibiting OSA than the general population.[94] The risk increases when the body mass index (BMI) is greater than 25 kg/m^2 at ages of 40 years or older.[94] The Wisconsin Sleep Cohort suggested the

prevalence of OSA to be 24% in 30- to 60-year-old CH patients,[95] much lower than other reports.[93,96] Also, with CH having a prevalence of approximately 50 cases per 100,000 people per year[80] and SRBDs occurring in approximately 20% to 25% of men,[18] it is quite apparent that not all people with a SRBD also have CH.

Headaches due to a SRBD are sometimes defined as a disorder of homeostasis, primarily caused by hypoxia and hypercapnia.[82] One suggested explanation for this relationship is that intracranial vasodilatation resulting from hypoxia and hypercapnia can produce a painful experience.[97] In addition, hypercapnia can induce activation of nociceptive afferents in the dura via vasodilatation.[98] During a cluster period, attacks can be precipitated by consumption of alcohol and other vasodilators such as histamine and nitroglycerine.[99] A history of tobacco smoking has been noted in up to 83% of male CH patients who average at least 20 cigarettes per day.[100] In 1984, Kudrow et al[101] found that approximately 60% of CH attacks came after hypoxic events, primarily during REM sleep. Chervin et al[93] found that 80% of their CH study group had an apnea-hypoxia index of greater than 5. Nobre et al[29] found the incidence of sleep apnea in CH patients to be 58.3% as compared to 14.3% in controls. CH and OSA are more common in men than in women.[29] As males reach puberty, the increase in testosterone production is thought to facilitate the collapsibility of the upper airway.[26] In healthy young men, the transition from wakefulness to sleep produces a decrease in ventilation and an increase in UARS.[102,103]

Meyer[104] reported a direct relationship between cerebral blood flow (CBF) and end-tidal volume pressure of CO_2. He suggested that hypoxia is a potent cerebral vasodilator that increases CBF via a decrease in production of prostacycline (a prostaglandin eicosanoid that prevents clotting and induces the dilation of blood vessels). This hypothesis was based on the observation that indomethacin will inhibit the vasoconstrictive effects of hyperoxia.[104] Potent vasodilators potentially influence changes in substances such as adenosine, a sleep-promoting agent.[104] Meyer also observed that in non-hyperventilation induced hypercapnia, CBF increased.[104] He reported that, as sleep initiates, there appears to be a progressive decrease in CBF. Also, with the onset of REM sleep, a marked increase in CBF is noted, particularly in the parieto-occipital regions of the cerebral cortex.

Sleep apneic patients demonstrate a more significant reduction in CBF during sleep than do their nonapneic counterparts, potentially leading to hypoxia of neural structures.[104] CBF has been demonstrated to increase during migraine and CH attacks.[104] May et al demonstrated an increase in blood flow in the area of the hypothalamus on the side ipsilateral to the head pain.[10,105] This same area of the hypothalamus, known as the anteroventral hypothalamic grey matter, also contains neurons of the SCN.[106] The SCN is known to be important in circadian rhythmicity.[107,108] This observation suggests that the SCN may be the site where CH is initiated.[109] Kudrow[110] suggested that the carotid body may play a significant role in the pathophysiology of CH. Their hypothesis views the CH attack period resulting from a dysfunctional hypothalamus, thereby creating a deregulation of vasomotor centers. They proposed that during the cluster period, chemoreceptive activity in the carotid body is blunted by inhibition of sympathetic vasomotor tone and by parasympathetic activation.

Conclusions

When only the anatomic and physiologic similarities of CH and SRBDs are considered, it would be tempting to suggest that they exist as a single disorder. While it is plausible that a SRBD will act as a trigger for CH attacks in cluster periods, not all CH patients exhibit a SRBD. If all CH attacks could be prevented with successful treatment of the comorbid SRBD, a stronger case could be made for a common etiology. In summary, when a CH patient is encountered in clinical practice, suspicion of a SRBD should lead the clinician to investigate further. With a good understanding of the commonalities of these disorders, the clinician's ability to care for these suffering individuals will only be enhanced.

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