Exploring the Connections Between Sleep and Cluster Headache

Poster #32

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PURPOSE

- The International Classification of Sleep Disorders recognizes four types of headaches related to sleep: cluster headache, hypnic headache, chronic paroxysmal hemicrania, and migraine.[1] The prevalence of cluster headaches is 0.1% and its etiology is unknown.[2] More men than women suffer from cluster headaches and patients typically exhibit wakefulness, agitation, and a desire to pace during paroxysmal bouts which are characterized by multiple headaches that remit and recur over the course of several hours or days.[3,4] Typically, a headache would last from 15 minutes to 3 hours, resolve spontaneously, and then recur, giving the condition its name of "cluster" headache. Cluster attacks are excruciatingly painful and differ from other types of headache in that the pain is periorbital, unilateral, and the episodes typically involve rhinitis, drooping eyelids, and lacrimation. People experiencing a cluster headache find no relief in sleep and may even prefer to pace or stand up.

- Unlike other sleep-related headaches, cluster headaches have a clear diurnal relationship (many patients arise with the headache) and seasonality, such that patients may have months of remission.[5] Some patients develop chronic cluster headaches which do not have such periods of remission. Headaches in general are associated with poor quality sleep,[6] but the association is quite pronounced in cluster headaches. People who suffer from any types of headache are also more likely to report symptoms associated with poor sleep, such as daytime fatigue and insomnia.[7,8] It has been speculated that cluster headaches may be a manifestation of a sleep disorder or that more complex sleep-related mechanisms are involved.[9]

- The purpose of this review is to examine the literature on cluster headaches and their relationship to sleep to present the current understanding by the medical community.

METHODS

- The authors searched the National Institutes of Medicine database, PubMed, for peer-reviewed medical literature on the subject by searching keywords: "sleep headache," "sleep-disordered headache," "sleep cluster headache," and "cluster headache." The articles were then evaluated to find those which offered insight into the relationship of sleep to cluster headache. In some cases, the bibliographies of relevant articles were searched for supplemental material. The result is a narrative review of the topic.

RESULTS

- Cluster headaches have three distinct pathophysiological stages: first, chronobiological aberrations impair the sympathetic nervous system.[5] Induction is stage two which is promoted by persistent dysfunction of the chemoreceptors accompanied by hypoxia, which may be caused by sleep apnea, vasodilatation, or some other cause. The third and final phase occurs with the signs and symptoms of the attack, resulting in trigeminal nerve stimulation with parasympathetic response. Thus, a neurological process starts the cascade of events that triggers the vasodilatation leading to the painful headache, with vasodilatation the result rather than the cause of trigeminal activation.[5]

- Most cluster headache patients report sleep as a headache trigger,[10,11] and they usually start about 90 minutes into a sleep cycle although the connection between a cluster headache and rapid-eye-movement sleep has been speculated but never established.

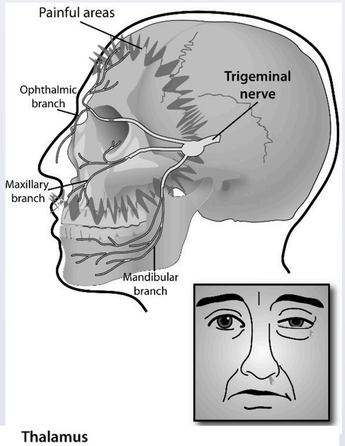

Fig. 1 The unilateral pain of cluster headache is associated with trigeminal nerve involvement and can result in severe pain, typically around one eye.

Art courtesy of Todd Cooper of Coyote Studios, Green Valley, California

- Cluster headaches often occur more frequently around summer and winter solstices, and it is speculated that the natural dark/light cycle may play a role as the differences are most pronounced at these times of year.

- Hypothalamic activation has been observed in brain scans of cluster headache patients during an attack.[12,13]

- Magnetic resonance imaging has shown that cluster headache patients have asymmetry of the hypothalamus gland and these patients have more grey matter in the hypothalamus than control patients.

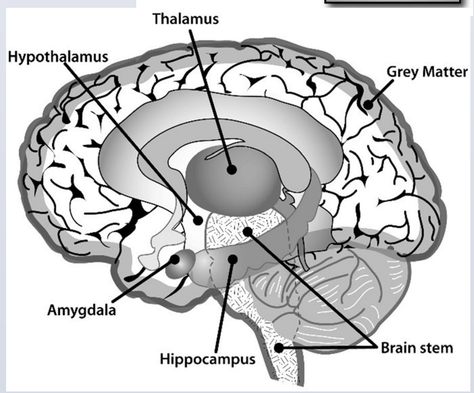

Fig. 2 The hypothalamus constitutes less than 1% of the brain by volume, but it is involved in numerous important processes, including regulation of the limbic system and regulation of the body's autonomic nervous system. It regulates arousal during sleep, the synthesis of many hormones, and the body's circadian clock. The nuclei in the brain stem and spinal autonomic ganglia receive afferent inputs from the periphery, which are delivered via the spinal cord and brainstem to the hypothalamus. The autonomic nervous system regulates the trigeminal nerves of the face which may play a role in headache pain as well as rhinorrhea, lacrimation, and nasal congestion associated with cluster headache.

Art courtesy of Todd Cooper of Coyote Studios, Green Valley, California

- The hypothalamus produced hypocretin (a neuropeptide) which is significantly lower in people with cluster headache than controls. Furthermore, melatonin which is produced by the pineal gland and secreted into the hypothalamus to promote sleep is not produced as much in cluster headache patients as others, particularly during attacks.[14]

- Finally, a study of sleep found that a healthy individual rouses out of sleep 7 to 15 times per hour although sleepers are rarely aware of these momentary arousals.[11] People with cluster headaches have fewer arousals during sleep, which has been suggested to be caused by reduced hypothalamic activity.

- Sleep-disordered breathing has been linked to certain headaches, but may not play a role in cluster headaches.[15] Apnea contributes to many forms of sleep-related headaches, but its association specifically to cluster headaches is unclear. Most people with cluster headaches do not get adequate treatment and many are never diagnosed at all.[16] In a survey, half of cluster headache patients said they would not tell their employer about their headache history for fear of losing their job.[17]

CONCLUSIONS

- The relationship between sleep and cluster headache has been well known for decades but remains to be more fully elucidated. It is tempting to see sleep as a cluster headache trigger, but the circadian and circannual periodicity of these headaches deserves special consideration. It appears as if cluster headaches involve an intricate synchronization of multiple factors: hypothalamic function in the brain, the light/dark cycle, sleep architecture, trigeminal inflammation, and the response of the autonomic nervous system. Since many people with cluster headache report getting them in their sleep and have a headache upon arising which is not relieved with sleep, cluster headaches were thought to be a form of sleep-related headache, such as migraine. However, evidence seems to suggest that cluster headaches are more likely a brain disorder than a problem with sleep or sleep-disordered breathing.

REFERENCES

1. Olesen J. The International Classification of Headache Disorders, 2nd edition: Application to practice. *Functional Neurology.* 2005;20:61-68.
2. Fischera M, Marziniak M, Gralow I. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalgia.* 2008;28:614-618.
3. Lund NLT, Snoer AH, Jensen RH. The influence of lifestyle and gender on cluster headache. *Current opinion in neurology, June 2019, Vol32(3), pp443-448.* 2019.
4. Baharav A, Shinar Z, Akselrod S, Mosek A, Davrath LR. Cluster headache patients have normal circadian and sleep time autonomic nervous system function. In: IEEE; 2005:263-266.
5. Kudrow L. The pathogenesis of cluster headache. *Curr Opin Neurol.* 1994;7(3):278-282.
6. Boardman HF, Thomas E, Millson DS, Croft PR. Psychological, Sleep, Lifestyle, and Comorbid Associations With Headache. *Headache: The Journal of Head and Face Pain.* 2005;45(6):657-669.
7. Jennum P, Jensen R. Sleep and headache. *Sleep Medicine Reviews.* 2002;6(6):471-479.
8. Paiva T, Batista A, Martins P, Martins A. The Relationship Between Headaches and Sleep Disturbances. *Headache: The Journal of Head and Face Pain.* 1995;35(10):590-596.
9. Paiva T. Sleep and headache. *Handbook of clinical neurology, 2011, Vol99, pp1073-1086.* 2011.
10. Barloese MCJ. Neurobiology and sleep disorders in cluster headache. *The Journal of Headache and Pain.* 2015(1):1.
11. Barloese MC, Jennum PJ, Lund NT, Jensen RH. Sleep in cluster headache - beyond a temporal rapid eye movement relationship? *Eur J Neurol.* 2015;22(4):656-e640.
12. May A, Bahra A, Buchel C, Frackowiak R, Goadsby P. Hypothalamic activation in cluster headache attacks. *Lancet.* 1998;352:275-278.
13. May A, Goadsby PJ. Cluster headache: imaging and other developments. *Curr Opin Neurol.* 1998;11(3):199-203.
14. Leone M, Lucini V, D'Amico D. Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. *Cephalalgia.* 1995;15:224-229.
15. Russell MB, Kristiansen HA, Kværner KJ. Headache in sleep apnea syndrome: Epidemiology and pathophysiology. *Cephalalgia.* 2014;34(10):752-755.
16. Schürks M, Kurth T, De Jesus J, Jonjic M, Rosskopf D, Diener HC. Cluster Headache: Clinical Presentation, Lifestyle Features, and Medical Treatment. *Headache: The Journal of Head and Face Pain, September 2006, Vol46(8), pp1246-1254.* 2006.
17. Palacios-Cena D, Talavera B, Lopez-Ruiz P, et al. Living With Cluster Headache: A Qualitative Study of Patients' Perspectives. *Headache, Jul/ Aug 2016, Vol56(7), pp1171-1182.* 2016.

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