

Circadian Rythms and Headache Disorders

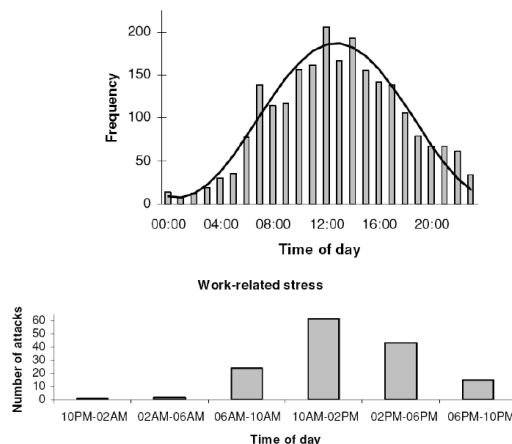
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Headache disorders and the circadian sleep-wake cycle are strongly related.¹ Primary headache disorders, such as migraine, hypnic headache, and cluster headache, occur with greater probability at certain times of the day and night, and a number of primary sleep disorders, notably obstructive sleep apnea, are associated with chronic headaches.

Sleep has a therapeutic effect on migraine attacks, and attacks are more likely to occur at certain times of the day. *Post hoc* analyses of clinical trials for sumatriptan show the highest risk of attacks at waking and during the morning hours.² Studies in Italian children confirmed a high morning risk but found that their attacks peaked in late afternoon.³ Among adults in arctic Norway, where ambient daylight is least constant throughout the year, migraine risk spikes in the morning but peaks at midday, which correlates with work-related stressors.⁴⁻⁷

Circadian Migraine in Arctic Norway

Frequency of attacks peaks with work-related stress



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For arctic Norwegian migraineurs with comorbid insomnia, diurnal migraine activity peaked during sleep hours, and attacks of migraine with aura increased during the constant daylight of summer months by comparison to winter months. These studies suggest that brain mechanisms involved in migraine interact with intrinsic circadian cycles and entraining cues, or *zeitgebers*, such as ambient light or social stressors.

Migraine and circadian disorders may be comorbid due to common genetic susceptibilities. We identified a family with five individuals, all of whom had a circadian

rhythm phenotype (advanced sleep phase syndrome⁸), migraine with aura, and a point mutation (T44A) in the serine/threonine protein kinase, casein kinase 1delta (CK1δ).^{9,10} Mice carrying the T44A mutation replicate the circadian phenotype and have physiological changes associated with migraine, including a reduced threshold for inducing cortical spreading depression and a heightened sensitivity to nitroglycerin-induced allodynia.^{11,12} The T44A mutation reduces the maximum reaction velocity of CK1δ for phosphorylation of hPer2 proteins¹⁰ (crucial to the function of intrinsic molecular clock mechanisms)^{13,14} and is the likely cause for the circadian phenotype seen in T44A mutant mice. A murine model of hemiplegic migraine with the R1920 mutation of the calcium channel, voltage-dependent, P/Q type, alpha 1A subunit gene shows changes in the ability to phase-shift to new ambient light/dark circadian cycles.¹⁵ This suggests that disorders of circadian dysregulation may be a common feature of migraine.

The timing of migraine attacks may also be related to sleep homeostatic factors.¹⁶ For example, adenosine has myriad roles in brain, including as an inhibitory neuromodulator and as a cerebral vasodilator,¹⁷ and it is often implicated as a putative sleep homeostatic factor.¹⁸ Plasma concentrations of endogenous adenosine rise during migraine attacks,¹⁹ and intravenous adenosine can precipitate a migraine attack.²⁰ Caffeine, an antagonist at two adenosine receptors, is a mild analgesic for headache that also causes cortical hyper-excitability and migrainous headaches after abrupt withdrawal from chronic exposure.⁹

In patients with cluster headache, a relationship to the onset of REM sleep (particularly with comorbid REM-associated obstructive sleep apnea) has been observed.²¹ Cluster periods tend to occur daily for several weeks to months, and they are more frequent in July and December,²² which suggests a relationship to the solstices, when the intrinsic molecular clock mechanisms of the suprachiasmatic nucleus (SCN) are maximally out of phase with ambient day/night *zeitgebers*. Attacks have been linked with increased metabolic activity and tissue density in a brain region posterior to the SCN that may lie within the posterior medial hypothalamus or the subparafascicular nucleus of the thalamus.^{23,24} It is unclear whether this abnormal diencephalic region is coincident with the major orexin-containing nuclei of the hypothalamus, but it is notable that a point mutation (G 1246A) in the orexin 2 receptor increases relative risk for cluster headache 6.8-fold,²⁵ and orexin deficiency is the hallmark of narcolepsy.

Hypnic headache is a primary headache disorder with strict onset of timing exclusively to the middle of the night, often with such predictability that it is called "alarm clock headache."²⁶ Hypnic attacks are not associated with migrainous or autonomic features.²⁷ Recently, a diencephalic region, possibly coincident with the region selectively active in cluster headache, has been shown to have reduced tissue density in patients with hypnic headache.²⁸

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