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Is Idiopathic Hypersomnia a Circadian Rhythm Disorder?

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Abstract

Purpose of review—The pathophysiology of idiopathic hypersomnia remains unclear, but some of its clinical features suggest the possibility of circadian dysfunction. This review will provide an overview of recent studies of circadian biology that have begun to elucidate the potential role of circadian rhythm dysfunction in idiopathic hypersomnia.

Recent findings—Clinically, people with idiopathic hypersomnia tend to have both a late chronotype and prominent sleep inertia or sleep drunkenness. Melatonin and cortisol profiles in people with IH confirm this tendency toward phase delay. More recently, it has been suggested that the night phase as defined by melatonin profile or period length as defined by BMA1 in dermal fibroblasts may also be prolonged in people with IH. Additionally, amplitude of melatonin rhythm and circadian gene expression, particularly BMAL1, PER1, and PER2, may be impaired in this disease.

Summary—Clinical features, melatonin profiles, and circadian gene expression all suggest abnormalities of the circadian system may be a contributor to the pathogenesis of IH.

Keywords

Idiopathic hypersomnia; circadian rhythm sleep wake disorders; delayed sleep phase syndrome; circadian rhythm genetics; sleep inertia; sleep drunkenness

I. Introduction

Idiopathic hypersomnia (IH) is a central disorder of hypersomnolence characterized by excessive daytime sleepiness that is not better explained by another disorder. In addition to sleepiness, there are several ancillary symptoms that are commonly present, including “sleep drunkenness”, long sleep times, prolonged non-refreshing naps, “brain fog” and hypovigilance. IH is diagnosed based on clinical history in combination with objective quantification of excessive daytime somnolence through the multiple sleep latency test, ad

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lib 24 hour polysomnography, or at least 7 days of ad lib actigraphy, after excluding other causes of sleepiness such as narcolepsy type 1, narcolepsy type 2, insufficient sleep syndrome, causal medical or comorbid psychiatric illnesses, and medication side effects [1]. Importantly, the diagnosis of IH requires exclusion of circadian rhythm sleep wake disorders that are causal to the symptoms of sleepiness, such as delayed sleep phase syndrome. However, as this review will highlight, there may still be aspects of circadian dysfunction present in people diagnosed with IH.

The etiology of IH is currently unknown and no single biomarker has been firmly established. However, there are several non-mutually exclusive, proposed hypotheses for its pathophysiology. Some of these hypotheses involve alterations of key wake-sleep regulatory pathways including mono-aminergic and GABAergic neurotransmitter systems, sleep-wake instability and disrupted sleep homeostasis [2, 3]. Other proposed mechanisms for IH include dysfunction of the autonomic nervous system and changes in the brain's default mode network or other regional changes in brain connectivity or metabolism [4-6].

Another important component of sleep-wake regulation is the circadian system. As our understanding of circadian rhythms has increased over the last few decades, the study of circadian function in idiopathic hypersomnia patients has become an intriguing possibility. There have been recent studies exploring circadian gene associations, expression of clock proteins and circadian phase mapping in patients with idiopathic hypersomnia. Although it is premature to conclude that IH is a circadian rhythm disorder, these studies provide increasing evidence that circadian dysfunction may contribute to at least some cases of IH. The aim of this review is to provide an overview of recent circadian studies in IH and to explore the role of circadian rhythm dysfunction in idiopathic hypersomnia.

II. Overview of the Circadian System

Many human activities, including numerous behavioral and metabolic processes, function on a diurnal cycle. Perhaps the most dramatic example of a diurnal cycle is the sleep-wake cycle, but other processes ranging from food intake to ovulation also exhibit clear diurnal cycles [7]. All of these processes are controlled by an internal timing system referred to as a circadian rhythm. The biological pacemaker for this process is the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus, and consists of neurons with self-sustained rhythmic properties. This endogenous rhythm typically has cycles of approximately, but rarely precisely, 24 hours [8].

Generation and maintenance of this circadian rhythm are accomplished by the expression of core circadian proteins that form an auto-regulatory transcriptional/translational feedback loop. The process starts during the biological daytime when two transcription factors, circadian locomotor output cycles kaput (CLOCK) and brain and muscle arnt-like protein 1 (BMAL1), form a heterodimer. This CLOCK-BMAL1 transcription factor complex binds to an enhancer box, promoting transcription of proteins including two key regulating proteins period (PER) and cryptochrome (CRY). As PER and CRY build up in the cytoplasm throughout the biological day, the proteins form a complex that travels back into the nucleus where it degrades the CLOCK-BMAL1 transcription factor. This inhibitory component

allows for the biological nighttime. PER and CRY concentrations decrease throughout the biological night, due to the degradation of CLOCK-BMAL1 complexes and an additional phosphorylation process, allowing this regulatory process to reset for the next biological day [9].

Clock gene expression is preserved across the majority of cell types and is found in both central and peripheral cells. Many peripheral cells exhibit rhythmic properties even in vitro (i.e., separated from the influence of the SCN), and these cells are considered part of the peripheral circadian clock [10, 9]. The SCN asserts dominant control over this system through endocrine and neuronal outputs, allowing for an orchestrated whole body clock. However, the presence of peripheral circadian clock cells provides an attractive and accessible way to investigate circadian genetics and function.

Because the endogenous circadian rhythm is rarely precisely 24 hours in length, the endogenous rhythm must be synchronized daily to the surrounding environment. Through a process called entrainment, the SCN uses inputs such as light to align its intrinsic cycle with the environment. Depending on the timing, duration and intensity of the light signal, exposure to light can cause either circadian phase advancement or delay [9].

Circadian phases can be mapped by measuring diurnal processes, such as temperature or hormones that are expressed in rhythm to the body's circadian cycle. Melatonin, a commonly measured circadian marker, is produced by the pineal gland, which has direct connections from the SCN. During the biological day, melatonin production is suppressed, resulting in a low melatonin concentration. This concentration begins to rise in the evening before peaking during the biological night. Dim light melatonin onset (DLMO), the time melatonin levels rise above baseline under dim light exposure, is an important measure of melatonin thought to represent the start of the biological night and typically occurs between 19:30 and 22:00 [11].

Sleep-wake processes are driven in part by the circadian rhythm. This endogenous rhythm promotes the expression of wake processes during the biological day and sleep processes during the biological night. Dysfunction of the circadian rhythm can present as a delayed or advanced onset of sleep, diminished amplitude, or impaired regulation of a circadian phase. The manifestations of these effects have a wide range of symptoms, and are important to investigate in IH.

III. Symptomatology of IH as a clue to circadian dysfunction

Idiopathic hypersomnia can have several clinical presentations, and current understanding of this syndrome is heavily influenced by case series of IH patients that have characterized the symptom profiles [12-21•]. While there is no single pathognomonic symptom, commonly reported symptoms of IH include long sleep times, prolonged non-refreshing naps, memory problems, attention deficits, automatic behaviors, and sleep drunkenness.

Although not considered as a part of the diagnostic criteria for the disorder, IH tends to be accompanied by a late chronotype. The three major chronotypes are early, intermediate, and late, where early type patients have a tendency to be alert in the morning and late type

patients have a tendency to be alert in the evening. A person's chronotype is thought to represent the behavioral phenotype of their underlying circadian processes. Numerous large genome wide association studies have shown an association of SNPs from key circadian genes with different chronotype presentations [22-24]. A commonly used grading scale is the Horne-Ostberg scale (HO), in which a lower score represents a later chronotype [25]. In one of the largest cohort studies of IH patients to date, Vernet et al reported that IH patients were significantly more alert in the evening with an HO score of 47.8, as compared to an HO score of 55.2 in controls [21•]. In a smaller sample, no significant difference in HO scores was seen between IH patients and controls (43.3 in IH vs 53.2 in controls, $p = 0.09$), but this may have reflected Type II error [26••].

Because of this tendency toward late chronotype, IH shares similarities to the circadian rhythm sleep-wake disorder, delayed sleep phase syndrome (DSPS). People with DSPS may also experience severe daytime sleepiness and pronounced sleep inertia. However, in DSPS these symptoms are attributed to chronic, partial sleep deprivation caused by a misalignment of chronotype and daily activities, e.g., needing to awaken in time for school or work. As such, DSPS patients should have resolution of sleepiness and sleep inertia with adjustment of their behavioral schedule to their circadian cycle. In contrast, while IH patients may have an evening chronotype, their symptoms would not be expected to abate with such alignment. DSPS symptomatology is from consequences of the internal circadian rhythm being misaligned with society's preferences, while IH patients continue to have symptoms despite increased sleep time or adjustment of their behaviors. At present, the precise mechanism of late chronotype in IH is still unknown.

An additional finding commonly shared between DSPS and IH is sleep drunkenness, the symptom of having great difficulty awakening from sleep, with prolonged cognitive dysfunction and lapses back into sleep. These symptoms are similar to sleep inertia, which is the physiologic transitional state between sleep and wake that is characterized by hypovigilance and impaired cognition. However, while sleep inertia is considered a normal biologic process, sleep drunkenness is considered pathologic, with much more severe symptoms. It is reported that 78% of IH patients have difficulty awakening with a reported range of 12.5 – 55.1% having sleep drunkenness [20•, 27••]. It is not currently known whether sleep drunkenness represents an exaggerated form of sleep inertia or represents a distinct process.

In healthy controls, sleep inertia is worsened with waking during the biological night [28]. In individuals with delayed sleep phase syndrome, sleep drunkenness occurs as a manifestation of phase delay, such that the difficulty awakening and propensity to fall back asleep arise from a person trying to awaken when their circadian rhythm is still in the biological night phase [1]. Thus, because IH patients tend to have a late chronotype, sleep drunkenness in IH patients could in part be explained by circadian misalignment. This is supported by the fact that lower HO scores are found in IH patients with sleep drunkenness than in patients without this symptom [20•]. However, if sleep drunkenness in IH was purely circadian, sleeping later into the environmental day resulting in awakening during the biological day would be expected to alleviate these symptoms, and daytime naps would not be expected to cause sleep drunkenness. However, increased total sleep time does not decrease sleep

drunkenness symptoms in IH patients and patients frequently report daytime naps are a trigger for sleep drunkenness [20•].

Thus, both sleep drunkenness and late chronotype symptoms in IH patients suggest that there may be an aspect of circadian dysfunction in IH, although such circadian dysfunction is unlikely to fully explain the phenotype.

IV. Measurement of Circadian Phase Timing and Duration in Idiopathic Hypersomnia

The first study to objectively measure circadian phases in idiopathic hypersomnia was by Nevsimalova et al in 2000, who measured salivary levels of both melatonin and cortisol to map circadian phases in IH and control patients [29••]. Salivary melatonin and cortisol had previously been shown to correlate well with serum melatonin, the gold standard for phase markers [30]. Salivary samples were taken over a 24 hour time period in a group of 15 patients with idiopathic hypersomnia with long sleep times and sleep drunkenness and 15 controls [29••]. IH patients had evidence for delayed circadian rhythms of both melatonin and cortisol. The evening melatonin rise was delayed by nearly 2 hours (occurring at a mean of 23:12 in IH patients and 21:32 in controls, $p < 0.01$). The morning decline was delayed by nearly 3 hours (8:41 in IH vs 5:56 in controls, $p < 0.01$). Morning cortisol rise was delayed by over an hour (5:31 in IH vs 4:22 in controls, $p < 0.01$). In addition to this evidence for phase delay in IH, the IH patients demonstrated significant lower nighttime melatonin concentration (21.3 pg/ml in IH vs 29.0 pg/ml in controls, $p < 0.05$). There was a suggestion that IH patients might have a longer duration of the night phase, as the length of the melatonin signal was longer by 91 minutes in IH patients than controls (9.68 hours in IH patients vs 8.17 hours in controls), but this finding was not statistically significant [29••].

A recent abstract has provided additional data in support of the idea that people with IH may have an abnormally long night phase duration, contributing to long sleep times and daytime sleepiness [31]. In this work, urine melatonin metabolites (urine 6-sulfatoxy melatonin) were measured in 50 IH patients, although control values were not provided. The average duration of biological night, as measured by urinary melatonin metabolites, was long at 16 +/− 1.2 hours. In only 10/50 (20%) patients, the biological night was considered to be of normal duration, i.e., 9 hours or less. Unspecified treatment response to bright light therapy occurred in 80% (32/40) of the patients with a baseline long biological night.

Recent breakthroughs in the understanding of dermal fibroblast cells have made it possible to directly investigate circadian phases in peripheral clock cells of IH patients. Dermal fibroblasts are peripheral clock cells and because circadian gene expression is preserved in these cells, the circadian phases in dermal fibroblasts can be used as surrogates for the circadian phases in central circadian clocks. Materna et al. examined the circadian period length of dermal fibroblasts in fifteen IH patients and compared them with sixteen healthy controls [26••]. Circadian period length of fibroblasts was measured using a lentiviral bioluminescence assay that transfected a luciferase gene under the control of BMAL1 promoter into human fibroblast cells. IH patients had significantly longer circadian period lengths than controls, by an average of 0.82 hours longer (average period length of 25.3

hours in IH patients vs 24.5 hours in controls; 95% CI for the difference of 0.44 to 1.2 hours).

V. Circadian Genetics in Idiopathic Hypersomnia

A case report identified a family that had three members with IH confirmed by clinical assessment and PSG, suggesting a genetic predisposition to IH in this family with an autosomal dominant inheritance pattern [32]. Other, larger studies have confirmed a predisposition to sleepiness in family members of IH patients, with affected family members in 26.9 to 39.1% of cases [17, 19, 33, 34]. Family predisposition, however, has been categorized largely by subjective accounts of daytime sleepiness in these relatives, as opposed to objective family diagnoses of IH.

To date, there have not been any published genetic association studies exclusively containing idiopathic hypersomnia patients. However, a few candidate–gene association studies have been performed on cohorts where large portions of the included patients met criteria for IH. One such study examined single nucleotide polymorphism (SNP) mutations in circadian genes with a cohort of patients with hypersomnia of central origin where 44.2% (38/86) of patients had idiopathic hypersomnia with long sleep time [35•]. Ten circadian SNPs (in CRY1, CRY2, and BMAL1) were investigated, and one SNP within CRY1 significantly differed between the central hypersomnia patients and controls. The frequency of this SNPs in the different included hypersomnia syndromes was not recorded, so it is unknown if this CRY1 gene polymorphism is independently associated with IH.

Dermal fibroblasts have also been used to investigate circadian genetic expression in IH and have produced intriguing evidence that key circadian genes are abnormally expressed in IH. Ten IH patients were chosen after rigorous diagnostic evaluation including clinical, PSG and MSLT assessment and dermal fibroblasts were obtained by skin biopsy [36••]. The expression of key circadian proteins was measured over two consecutive 24-hour periods and compared to concentrations in a healthy control group. The circadian amplitudes of the expressed genes BMAL1, PER1 and PER2 were decreased in fibroblasts of IH patients as compared to that of healthy controls. The largest decrease was in the BMAL1 gene, in which the amplitude of expression was decreased by 63% in the first diurnal cycle and by 46% in the second cycle. PER1 and PER2 gene expression were also were also decreased in the first diurnal cycle by 45% and 32%, respectively. CRY1 and CRY2 expression did not differ between IH and control samples. The only difference in gene transcription rate for the two groups was in BMAL1, which was significantly lower in IH patients than controls [36••].

Despite the many similarities between central and peripheral clock cells, differences in expression as well as function of certain genes are thought to exist [10]. Therefore, we cannot extrapolate whether the central circadian clock cells in IH also exhibit the impaired circadian gene expression found in fibroblast cells. Additionally it is still unclear whether the altered expression of clock genes is due to genetic mutations or instead due to disrupted sleep, as it has recently been shown that disrupted sleep may alter fibroblast circadian gene expression [37].

Nonetheless, the demonstration of impaired gene expression of circadian protein BMAL1, and to a lesser extent circadian proteins PER1 and PER2, in fibroblasts of IH patients identify possible molecular drivers of the previous findings of delayed and prolonged circadian phases in IH.

VI. Conclusion

Idiopathic hypersomnia is a central disorder of hypersomnolence that is associated with late chronotype and sleep drunkenness. Clinical phenotype and melatonin and cortisol rhythms are consistent with a circadian phase delay. A longer circadian period or longer night phase is suggested by studies of dermal fibroblasts and urinary melatonin metabolites, respectively. Decreased circadian amplitude is seen in both melatonin levels and expression of circadian genes BMAL1, PER1, and PER2. A SNP within circadian gene CRY1 is associated with the central disorders of hypersomnolence as a group, including idiopathic hypersomnia. Further investigation is needed to better understand the disrupted circadian phases and altered gene expression observed in idiopathic hypersomnia patients and whether these are playing a causative role in symptoms.

Research Agenda:

- **a.** Determine the mechanisms of the symptoms of sleep drunkenness and late chronotype in IH. A study comparing the evening rise and morning decline of melatonin between IH patients with and without a late chronotype as well as IH patients with and without sleep drunkenness would examine if these symptoms are from a delayed night phase.
- **b.** Determine underlying pathophysiology behind the delayed and prolonged night phase. While BMAL1 appears to play an important role in IH, it may be that key transcriptional regulators of BMAL1, as opposed to mutations of the BMAL1 gene, are the driver as the expression of BMAL1 rather than protein function has been found to be abnormal.
- **c.** Examine if using circadian rhythm therapies improve symptoms as well as improve phase delay in IH patients.

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