Non–24-Hour Sleep–Wake Syndrome in Sighted and Blind Patients

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KEYWORDS

- Circadian rhythm sleep disorders
- Non–24-hour sleep–wake disorder
- Free-running type • Non-entrained type
- Hypernychthemeral syndrome • Blindness
- Melatonin

NON–24-HOUR SLEEP–WAKE SYNDROME (CIRCADIAN RHYTHM SLEEP DISORDER, FREE-RUNNING TYPE, NON-ENTRAINED TYPE, HYPERNYCHTHEMERAL SYNDROME)

Non–24-hour sleep–wake syndrome (N24HSWS) is defined as a ''complaint of insomnia or excessive sleepiness related to abnormal desynchronization between the 24-hour light/dark cycle and the endogenous circadian rhythm of sleep and wake propensity.''[1,2] The daily light/dark cycle is the most powerful environmental time cue for synchronizing the hypothalamic circadian pacemaker to the 24-hour day. Individuals who are physically or biologically isolated from a normal 24-hour light/dark cycle exhibit a sleep/wake cycle that is different from, and usually longer than, 24 hours.[3,4] This non–24-hour cycle leads to progressively later or progressively earlier bedtimes and wake times. N24HSWS is a rare condition in sighted individuals and is characterized by a chronic steady pattern of typically approximately 1-hour delays in spontaneous sleep onset and wake times while living under normal environmental conditions.[1] Because most individuals usually are required to live on a 24-hour social day and maintain a regular sleep–wake schedule, the sufferer displays periodically recurring problems with sleep initiation, sleep maintenance, and rising, as the circadian cycle of wakefulness and sleep propensity moves in and out of synchrony with the fixed social sleep episode.[5] Although the disorder is generally rare in sighted people, there are a considerable number of reports of N24HSWS in sighted subjects,[5,6] and a recent review indicated that the disorder may be more common than previously thought in individuals in their teens and 20s.[6]

N24HSWS is most common in individuals who are totally blind;[1,5,7] as many as half of totally blind patients have this disorder. In these patients, the lack of ocular light information reaching the circadian pacemaker prevents the pacemaker from entraining to the normal 24-hour light/dark cycle.[7] Consequently, the circadian pacemaker reverts to its endogenous non–24-hour period, causing a chronic, cyclic sleep–wake disorder characterized by episodes of good sleep followed by periods of poor sleep and excessive daytime sleepiness, followed by good sleep, ad infinitum. There are some differences, however, between sighted and blind subjects in the etiology and expression of this disorder. This article reviews the clinical aspects and pathophysiology of

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sighted and blind patients suffering from N24HSWS.

CLINICAL CHARACTERISTICS OF NON–24-HOUR SLEEP–WAKE SYNDROME IN SIGHTED PATIENTS

The prevalence of N24HSWS in the general population has not been established, but it is assumed to be rare.[1] Systematic clinical examinations of sighted patients who have N24HSWS also are relatively rare, although many single-case reports have been described (**Table 1**).[8–34]

Clinical Features

The basic characteristics of sighted patients who have N24HSWS (eg, sex, age, and age at onset) remain to be elucidated.[1] Hayakawa and colleagues[6] examined 57 consecutively diagnosed sighted patients who had N24HSWS and found that 72% of them were men. This finding is consistent with previous studies listed in **Table 1**, in which 85% of the patients were male. The commencement of a free-running sleep/wake cycle usually occurred when patients were in their teens or 20s (see **Table 1**). Nearly all the patients (98%) had a history of disturbed social functioning resulting from the inability to attend school or work regularly, and about a quarter (28%) had psychiatric disorders.

Sleep Features

By definition, a non–24-hour sleep–wake pattern is characteristic of this disorder and usually is defined by data from daily sleep logs and/or wrist actigraphy collected over several consecutive weeks. Sleep duration tends to be normal to long with a mean (± SD) sleep duration of 9.3 hours (± 1.3 hours) and a median duration of 9.0 hours.[6] Polysomnography typically has not been performed or reported in detail in such patients, because sleep structure and quality on a given single-night recording depend on the phase relationship between internal biologic time and sleep.[35]

Fig. 1 shows representative self-reported sleep–wake records for three patients who had N24HSWS: a 26-year-old woman (see **Fig. 1**A, case 1), a 22-year-old man (see **Fig. 1**B, case 2),[6] and a 30-year-old man (see **Fig. 1**C, case 3).[8] All subjects began exhibiting symptoms in their teens and had difficulty adjusting to school and college schedules. Clinical examinations failed to reveal any abnormalities in routine electroencephalogram, MRI, hematology, or biochemistry tests. Semistructured psychiatric interviews revealed that case 1 had an adjustment disorder and case 2 suffered from major depression (according to *Diagnostic and Statistical Manual edition 4* criteria). Case 3 had no Axis I or III disorders. Although the sleep/wake cycle clearly has a non–24-hour pattern in all three cases, the behavior is not identical. Case 1 shows a relatively steadily delaying free-running sleep pattern, albeit with some occasional minor changes in sleep duration. This pattern can be expressed only in those patients without strong social commitments (eg, work or school) that would prevent sleep during the daytime hours. Cases 2 and 3 show more typical patterns, although they also result in substantial social isolation. In both cases, the sleep/wake cycle does not simply have a constant non–24-hour pattern; there are at least two distinct components that repeat cyclically. The sleep/wake cycle shows a regular ‘‘free run’’ when sleep is initiated during the night or early morning, close to a normal social sleep time and when natural sunlight is not available, although most sleep episodes still start during the night (see **Fig. 1**C, *middle panel*). Once the sleep onset has delayed into the morning hours, the sleep/wake cycle becomes more disrupted and seems to delay more rapidly or to have a series of delayed-phase ‘‘jumps.’’ These jumps tend to occur when sleep onset approaches 8:00 to 10:00 AM; sleep onset rarely occurs between 10:00 AM and 4 PM (see **Fig. 1**B and C).

Such phase jumps occur in about half of patients who have N24HSWS (54%) and result in a longer observed sleep–wake period on average (26.1 ± 0.8 hours) than observed in those who do not exhibit such changes (24.9 ± 0.5 hours). The non-uniform distribution of the sleep–wake behavior and the fact that sleep tends to become more abnormal when it coincides with the light phase of the day suggests that the free-running sleep/wake cycle of these patients is influenced by the timing of the light/dark cycle. As discussed later, several experimental protocols provide support for this conclusion. Rapid changes in the phase of the sleep/wake cycle also are observed in some totally blind subjects who have N24HSWS, however, suggesting a potential role for nonphotic or social cues in altering sleep–wake behavior in these patients.

N24HSWS and delayed sleep phase disorder (DSPD) may share a common pathology, and persistent sleep phase delay may increase the risk of the occurrence of N24HSWS.[21,36] For example, Oren and Wehr[21] reported that two patients who had DSPD had developed N24HSWS after chronotherapy in which their sleep phase was scheduled to be delayed by 3 to 4 hours in an attempt to obtain the desired sleep