

Non-24-Hour Sleep-Wake Rhythm Disorder in Sighted and Blind Patients



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KEYWORDS

- Circadian rhythm sleep disorders • Non-24-hour sleep-wake rhythm disorder • Free-running type
- Nonentrained type • Hypnnychthemeral syndrome • Blindness • Melatonin

KEY POINTS

- Non-24-hour sleep-wake rhythm disorder (N24SWD) is a debilitating cyclic circadian rhythm sleep disorder characterized by an inability to sleep on a 24-hour schedule.
- N24SWD is rare in sighted individuals and has multiple possible causes including behavioral, sleep-wake regulation or genetic causes.
- N24SWD is highly prevalent in totally blind individuals due to a lack of light information reaching the circadian clock.
- Optimal treatment should reset the underlying nonentrained circadian pacemaker. There are currently no approved treatments for sighted patients with N24SWD although structured light therapy and melatonin treatment hold promise.
- Tasimelteon (20 mg at a fixed clock time each day), a dual melatonin receptor agonist, was recently approved to treat N24SWD in totally blind patients.

NON-24-HOUR SLEEP-WAKE RHYTHM DISORDER (FREE-RUNNING DISORDER, NONENTRAINED DISORDER, HYPERNYCHTHEMERAL SYNDROME)

Non-24-hour sleep-wake rhythm disorder (N24SWD) is defined as a “history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, owing to misalignment between the light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-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. N24SWD is a rare condition in sighted individuals and is characterized by a chronic steady pattern of delays, typically of approximately 1 hour per day in spontaneous sleep-onset and wake times while living under

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normal environmental conditions.¹ As most individuals are usually 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^{5,6}; and the disorder may be more common than previously thought in individuals in their teens and 20s.⁶

N24SWD is most common in individuals who are totally blind,^{1,5,7,8} with as many as one-half of totally blind patients having this disorder. In such patients, the lack of ocular light information reaching the circadian pacemaker prevents it 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 episodes 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. We review the clinical aspects and pathophysiology of the sighted and blind patients suffering from N24SWD.

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

The prevalence of N24SWD in the general population has not been established, but it is presumed to be rare.¹ Systematic clinical examinations of sighted patients with N24SWD are also relatively rare, although many single case reports have been described (Table 1).^{9–35}

Clinical Features

The basic characteristics of sighted patients having N24SWD, such as sex, age, or age at onset, remain to be elucidated.¹ Hayakawa and colleagues⁶ examined 57 consecutively diagnosed patients with sighted N24SWD and found that 72% of them were men. This is comparable with previous studies listed in Table 1, where 85% of the patients were male. The commencement of a non–24-hour sleep–wake cycle occurred mostly when patients were in their teens or 20s (see Table 1). Nearly all of the patients (98%) had a history of disturbed social functioning owing to inability to regularly attend school or work and about one-quarter (28%) had psychiatric disorders.

Sleep Features

By definition, a non–24-hour sleep–wake pattern is characteristic of this disorder and is usually defined from daily sleep logs and/or wrist actigraphy collected over several consecutive weeks. Sleep duration tends to be normal to long with a mean (\pm standard deviation) sleep duration of 9.3 ± 1.3 hours and a median of 9.0 hours.⁶ Polysomnography has typically not been performed or reported in detail in such patients because sleep structure and quality on a given single night recording depends on the phase relationship between internal biological time and sleep.³⁶

Fig. 1 shows representative examples of self-reported sleep–wake records in 3 patients with N24SWD; a 26-year-old woman (see Fig. 1A), a 22-year-old man (see Fig. 1B),⁶ and a 30-year-old man (see Fig. 1C).⁸ All subjects began exhibiting symptoms in their teens and had difficulty with adjusting the school and college schedules. Clinical examinations failed to reveal any abnormalities in routine electroencephalogram, MRI, hematology and biochemistry tests. Semi-structured psychiatric interviews revealed that case 1 had adjustment disorder and case 2 suffered from major depression (according to DSM-IV criteria). Case 3 had no axis I or III disorders. Although the sleep–wake cycle clearly has a non–24-hour pattern in all 3 cases, the behavior is not identical. Case 1 shows a relatively steadily delaying free-running sleep pattern, albeit with some minor changes in sleep duration occasionally. This pattern can only be expressed in those without strong social commitments (eg, work, 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 2 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. 1C, 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 have a series of delayed phase “jumps.” This jump tends to occur when sleep onset approaches 8 to 10:00 AM; sleep onset occurs rarely between 10:00 and 16:00 hours (see Fig. 1B and C).

Such phase jumps occur in about one-half of patients (54%) with N24SWD and results in a longer observed sleep–wake period on average

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