Circadian Rhythm Sleep Disorder: Irregular Sleep Wake Rhythm

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KEYWORDS

• Circadian • Rhythm • Neurodegeneration
• Alzheimer's disease • Irregular

Most physiologic, hormonal, and behavioral processes, most notably the sleep–wake cycle, exhibit nearly 24-hour (circadian) rhythms. These endogenous circadian rhythms are generated by the suprachiasmatic nucleus (SCN), a paired nucleus in the hypothalamus of the brain.[1–3] In humans, light is the strongest entraining agent for the circadian clock,[4] but nonphotic stimuli such as physical activity[5] and endogenous melatonin[6] also can alter the timing of circadian rhythms. In addition to its role in the timing and synchronization of biologic rhythms, the circadian pacemaker promotes alertness during the day and thus facilitates the consolidation of nocturnal sleep and daytime wakefulness across the 24-hour cycle.[7–11]

Significant changes in circadian regulation occur with aging and probably contribute to the higher prevalence of irregular sleep–wake rhythm disorder (ISWRD) in older adults. ISWRD is characterized by the relative absence of a circadian pattern in an individual's sleep–wake cycle. Common age-associated changes in circadian rhythm are the decreases in the amplitude of physiologic (eg, core body temperature) and hormonal circadian rhythms.[12–16] These age-related changes may be the result of degeneration or decreased neuronal activity of SCN neurons, decreased responsiveness of the circadian clock to entraining agents such as light, and decreased exposure to bright light and structured social and physical activity during the day.[17–20]

Alterations in the central regulation of circadian rhythms when combined with the decreased levels of light exposure and social/physical activity levels probably contribute to the increased prevalence of ISWRD in older adults. This tendency toward increased prevalence of ISWRD is often further exaggerated in older adults who have neurodegenerative disorders, such as Alzheimer's disease.[21]

CIRCADIAN RHYTHM SLEEP DISORDER, IRREGULAR SLEEP–WAKE RHYTHM TYPE (ALSO KNOWN AS IRREGULAR SLEEP–WAKE RHYTHM DISORDER)

Consolidation of nocturnal sleep and daytime alertness is achieved when the desired sleeping and waking times are synchronized with the timing of the endogenous propensity for a circadian rhythm of sleeping and waking. Although the primary pathophysiology of irregular sleep–wake rhythm (ISWR) is caused by a disruption of circadian timing, its actual clinical presentation also is influenced by a combination of behavioral and environmental factors.

Clinical Features and Diagnosis

ISWRD is characterized by the lack of a clearly defined circadian sleep–wake rhythm in which sleeping and waking periods are distributed in at

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least three short bouts (lasting 1–4 hours) throughout the 24 hours, but the total amount of sleep obtained over a 24-hour period is generally normal for the age of the patient (**Fig. 1**).[22] Although sleeping and waking periods are fragmented, the longest sleep period usually is between 2 and 6 AM.[23] Daytime sleep often is composed of multiple naps, whereas nighttime sleep is severely fragmented and shortened. Consequently the primary symptoms of ISWRD are chronic sleep-maintenance insomnia and excessive daytime sleepiness. Diagnosis is made by the clinical history of fragmented sleeping and waking periods along with chronic complaints, usually of sleep-maintenance insomnia and excessive daytime sleepiness. In addition, a sleep diary and/or actigraphy for at least 7 days should be undertaken and show at least three irregular intervals of sleeping and waking periods within a 24-hour period.[22]

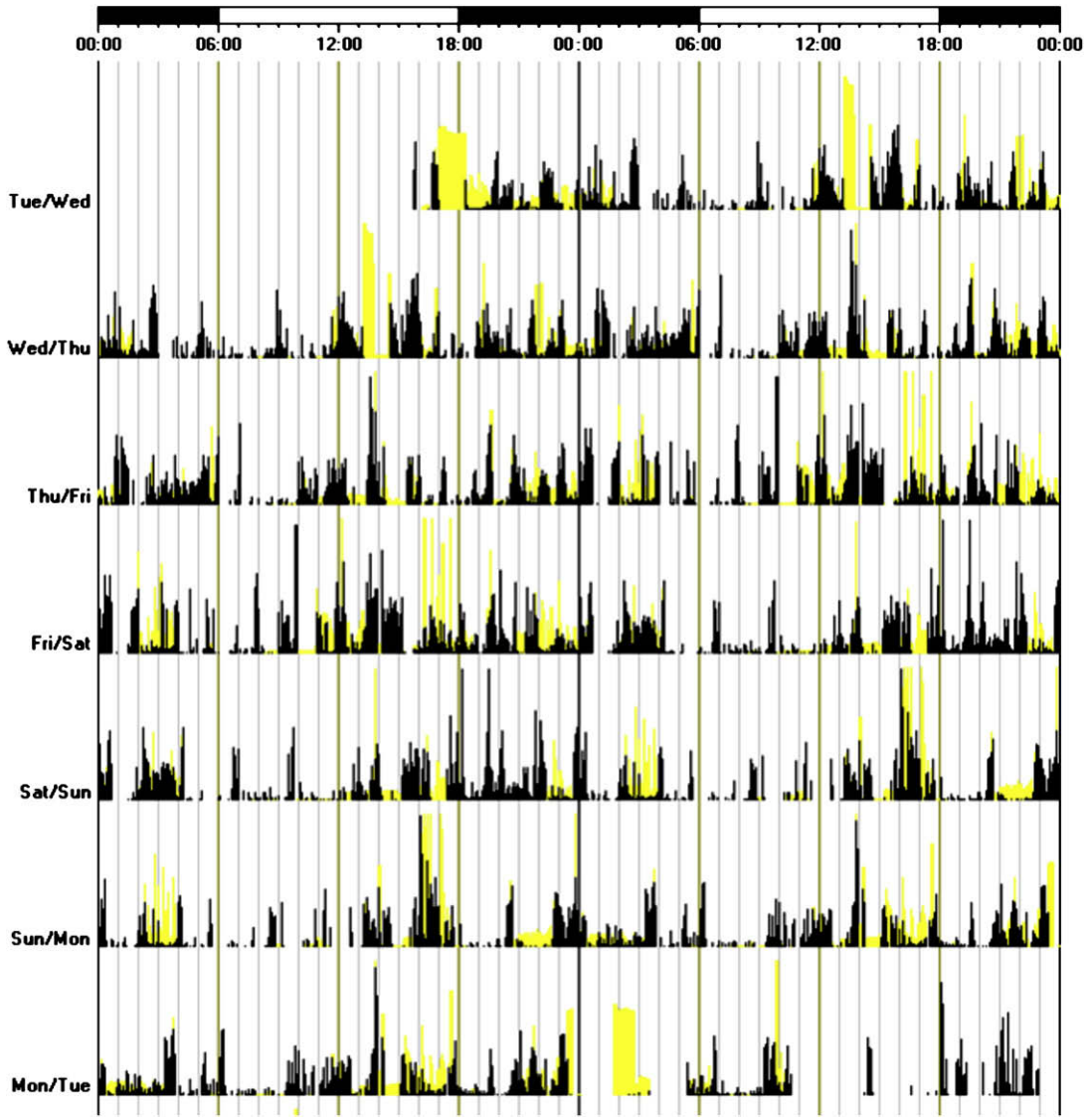

Fig. 1. Actogram obtained by actigraphy over a 7-day period from an older adult patient who has ISWRD. The yellow bars indicate timing and level of ambient light exposure, and the black bars indicate activity levels recorded at the nondominant wrist. Note the lack of a discernible circadian sleep–wake rhythm. Sleep is characterized by nocturnal fragmentation and multiple short periods of sleeping and waking across the entire 24-hour day.

Epidemiology

Although the prevalence of ISWRD increases in later life, age itself is not an independent risk factor for ISWRD. Rather, the age-associated increases in medical, neurologic, and psychiatric disorders have been shown to be the greatest contributors to the development of ISWRD.[24] The disorder is seen more commonly in institutionalized older adults and most commonly in patients who have Alzheimer's disease.[24] Other disorders of the central nervous system, including traumatic brain injury and mental retardation, also can lead to an ISWR pattern.[23,25–27]

Pathophysiology

It has been postulated that both dysfunction of the central processes responsible for the generation of the circadian rhythm and decreased exposure to external synchronizing agents termed ''zeitgebers'', such as light and social activities, play a role in the development and maintenance of ISWR. The findings of age-related loss of neurons and functional changes within the SCN[17] and a further decrease in the number of neurons within the SCN in patients who have Alzheimer's disease[28,29] suggest that neurodegeneration of the SCN may contribute to the development of ISWRD in older adults.

Older adults, especially those who have chronic medical and neurologic disorders, often are exposed to lower levels of daytime light than their younger counterparts.[30,31] This reduction may be exacerbated by age-related visual disorders, such as cataracts, which can further attenuate the effect of ambient light on the SCN. The impact of diminished exposure to circadian synchronizing agents such as light and activity is most pronounced in patients who have Alzheimer's disease. Low light levels and lack of structured social and physical activities in long-term care facilities may decrease further the amplitude of circadian rhythms. In fact, lower daytime light levels are associated with an increase in nighttime awakenings, even after controlling for the level of dementia.[32]

Finally, although there is no direct evidence for a genetic basis for ISWRD, several lines of evidence suggest that the sleep disturbance seen in Alzheimer's disease is at least partially based on genetic factors. Actigraphic studies of patients who have Alzheimer's disease have demonstrated longitudinal deterioration of sleep quality,[33,34] and most of this longitudinal variance in sleep seems to be related to an inherent trait of the individual patient. This evidence suggests that genetic factors may help determine the ultimate course and level of sleep deterioration seen in a given patient who has Alzheimer's disease,[35,36] a hypothesis consistent with considerable research suggesting that much of the circadian variation in many physiologic systems is controlled by a limited number of similar genes across species.[37] Further studies are needed to determine if certain mutations or polymorphisms of circadian clock genes play a role in the development of ISWR.

Treatment

The primary goals of treatment of an ISWR are to consolidate sleep during the night and wakefulness during the day. To this end, measures aimed at restoring or enhancing exposure to the various SCN time cues or zeitgebers are critical. Patients should be exposed to bright light during the day, and bright light should be avoided in the evening and at night.[38,39] Daytime physical and social activities also should be strongly encouraged.[40–43] A multicomponent approach using a variety of behavioral treatment options is recommended.

Light

The overall approach to light therapy for the treatment of the ISWR type is to increase both the duration and intensity of light exposure throughout the daytime and to avoid exposure to bright light in the evening. Bright light exposure delivered for 2 hours in the morning at 3000 to 5000 lux over the course of 4 weeks has been found to decrease daytime napping and increase nighttime sleep in demented subjects.[44] Light may help further consolidate nighttime sleep, decrease agitated behavior, and result in stronger amplitudes of the circadian rhythm.[38,39,44]

Melatonin

When compared with the effects of bright light, studies evaluating the use of melatonin in ISWRD have yielded less consistent results.[24] Serfaty and colleagues[45] randomly assigned 44 participants who had a *Diagnostic and Statistical Manual-IV* diagnosis of dementia and comorbid sleep disturbance to a 7-week double-blind crossover trial of 2 weeks of slow-release melatonin (6 mg) versus placebo. It should be noted that only 25 of the 44 patients completed the trial. Melatonin had no effect on actigraphically measured total sleep time, number of awakenings, or sleep efficiency. Another large scale trial of 157 patients who had Alzheimer's disease found no statistically significant differences in actigraphy-derived sleep measures between a control group and those taking 2.5 mg melatonin,[46] although a trend toward improvement was seen with 10 mg melatonin. Overall, the

efficacy of melatonin treatment for circadian and sleep disorders remains undetermined (for review, see Brzezinski and colleagues[47]).

Some success, however, has been shown in small studies in using melatonin to treat sleep disturbances in children who have psychomotor retardation and presumed ISWR.[48] Significant, although incomplete, benefit also was reported in an open-label trial of melatonin, 2 to 20 mg, given at bedtime to children who had varied neurologic disabilities and chronic sleep–wake cycle disorders.[49,50] Furthermore, a more recent study indicates that a controlled-release melatonin formulation may be more effective for sleep maintenance than the immediate-release formulation in a similar population.

Other therapeutic approaches

Structured physical activity and social activity may help provide temporal cues to increase the regularity of the sleep–wake schedule. Allowing for a favorable sleep environment by reducing nighttime light and noise and improving incontinence care can reduce awakenings in nursing home residents.[51] Furthermore, Alessi and colleagues[52] documented that elderly subjects reported decreased daytime sleep and increased participation in social and physical activities and social conversation by following a regimen of reduced time in bed during the day, a structured bedtime routine at night, 30 minutes or more of sunlight exposure a day, and increased physical activity.

The use of a multimodal nonpharmacologic approach including an increase in sunlight exposure and social activity during the day and a decrease in daytime in-bed time and nighttime noise may be particularly effective. A recent randomized, controlled trial testing such an approach was conducted recently in a group of community-dwelling patients who had Alzheimer's disease with inferred ISWRD diagnoses.[53] Thirty-six community-dwelling patients who had Alzheimer's disease and their family caregivers participated. All participants received written materials describing age- and dementia-related changes in sleep and standard principles of good sleep hygiene. Caregivers in active treatment received specific recommendations about setting up and implementing a sleep hygiene program for the dementia patients and training in behavior management skills. Patients in active treatment also were instructed to walk daily and to increase daytime light exposure with the use of a light box. Control subjects received general dementia education and caregiver support. Sleep was measured actigraphically. Patients in the active-treatment arm showed significant reductions in number of nighttime awakenings and total time awake at night compared with control subjects. At 6-month follow-up, treatment gains were maintained, and additional significant improvements in the duration of night awakenings and circadian organization of sleep emerged.

The most effective ISWRD treatments seem to require a combination of structured social and physical activity, exposure to light during the day, and minimizing nighttime light and noise.[39,51,54,55] A more recent study, however, showed that light alone did not improve nocturnal sleep, but that a combination of light and melatonin (5 mg) increased daytime waking time and activity levels and also strengthened the rest–activity rhythm in patients who had Alzheimer's disease.[56] Riemersma-van der Lek and colleagues[57] found that exposure to bright light during the day had a modest benefit in improving cognitive function and mood, whereas 2.5 mg of melatonin taken in the evening shortened sleep latency and increased sleep duration but adversely affected mood in elderly residents of group-care facilities. Therefore, the authors concluded that melatonin should be used only in combination with light. In this same study, a combined treatment with light and melatonin decreased aggressive behavior and modestly improved sleep efficiency and decreased nocturnal restlessness.

SUMMARY

Individuals who have ISWRD often present with symptoms of sleep-maintenance insomnia and excessive daytime sleepiness. ISWR always should be considered in the differential diagnosis of sleep disturbances in older adults and in children who have neurologic impairments. It is commonly accepted that a combination of dysfunction of the circadian clock (SCN) and decreased exposure to circadian zeitgebers, such as timed bright light and structured physical or social activities, have important roles in the development and maintenance of the characteristic irregular low-amplitude circadian sleep–wake rhythm of ISWRD. Studies of the effectiveness of pharmacologic treatments for ISWRD generally have yielded negative or inconsistent results. One exception may be in children who have psychomotor retardation, in which melatonin has been shown to improve the sleep–wake pattern. Furthermore, the safety of pharmacologic agents has not been well studied, particularly in the elderly, who are more likely to suffer from ISWRD. Therefore, a mixed-modality behavioral approach to consolidate nocturnal sleep (improved sleep hygiene; decreased nocturnal light and noise levels) and enhance daytime alertness (increased

daytime light exposure; increased social and physical activity) is the mainstay treatment for ISWRD. The success of treatment for this condition is highly variable and requires tailoring to individual needs. It is expected that rapid advances in the understanding of the genetic regulation of circadian rhythms will define better the genetic vulnerability for ISWRD and should lead to prevention and improved treatment of this circadian-based disorder.

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