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Circadian Rhythm Sleep Disorder: Irregular Sleep Wake Rhythm Type

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Abstract

Irregular Sleep Wake Rhythm Disorder (ISWRD) is characterized by the relative absence of a circadian pattern in an individual's sleep-wake cycle. Significant changes in circadian regulation occur with aging and with neurodegenerative diseases, such as Alzheimer's disease prevalent in older adults, which are likely to contribute to the prevalence of ISWRD seen in these populations, although ISWRD is also seen in traumatic brain injury and mental retardation populations. ISWRD is thought to result from some combination of; degeneration or decreased neuronal activity of suprachiasmatic nucleus (SCN) neurons, decreased responsiveness of the circadian clock to entraining agents such as light and activity, and decreased exposure to bright light and structured social and physical activity during the day. Treatment of ISWRD seeks to consolidate sleep during the night and wakefulness during the day; primarily through restoring or enhancing exposure to the various SCN time cues, or "zeitgebers". Studies of the effectiveness of pharmacologic treatments for ISWRD have generally yielded negative or inconsistent results. In general multi-modal non-pharmacological approaches involving increased exposure to light, increased physical and social activities and improved sleep hygiene have been the most successful therapeutic approaches.

INTRODUCTION

The majority of physiological, hormonal and behavioral processes, most notably the sleep wake cycle, exhibit near-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 non-photic stimuli such as physical activity [5] and endogenous melatonin [6] can also alter the timing of circadian rhythms. In addition to its role in the timing and synchronization of biological 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 likely contribute to the higher prevalence of irregular sleep wake rhythm disorder (ISWRD) in older adults. ISWRD is

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characterized by the relative absence of a circadian pattern in an individual's sleep-wake cycle. Common age-associated circadian rhythm changes are the decreases in amplitude of physiological (e.g.; 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 likely contribute to the increased prevalence of ISWRD in older adults. This tendency towards increased prevalence of ISWRD seen in older adults is often further exaggerated in older adults with neurodegenerative disorders, such as Alzheimer's disease. [21].

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

Consolidation of nocturnal sleep and daytime alertness is achieved when the desired sleep and wake times are synchronized with the timing of the endogenous circadian rhythm of sleep and wake propensity. While the primary pathophysiology of ISWR is due to a disruption of circadian timing, its actual clinical presentation is also 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 sleep and wake periods are distributed in at least 3 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 (Figure 1). [22] Although sleep and wake periods are fragmented, the longest sleep period is usually between 2–6 AM [23]. Daytime is often 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 sleep and wake periods along with chronic complaints of usually sleep maintenance insomnia and excessive daytime sleepiness. In addition, sleep diary and/or actigraphy for at least seven days should be performed and show at least 3 irregular intervals of sleep and wake periods within a 24-hour period. [22]

Epidemiology

While the prevalence of ISWRD increases in later life, age itself is not an independent risk for ISWRD. Rather, the age associated increase in medical, neurological and psychiatric disorders have been shown to be the greatest contributors to the development of ISWRD. [24] The disorder is more commonly seen in institutionalized older adults and most commonly in patients with Alzheimer disease. [24] However, other disorders of the central nervous system, including traumatic brain injury and mental retardation can also lead to an irregular sleep-wake rhythm pattern. [23,25–27].

Pathophysiology

It has been postulated that both dysfunction of the central processes responsible for the generation of the circadian rhythm as well as decreased exposure to external synchronizing agents, or "zeitgebers", such as light and social activities play a role in the development and

maintenance of irregular sleep-wake rhythms. 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 with Alzheimer disease (AD) [28,29] suggest that neurodegeneration of the SCN may contribute to the development of ISWRD in older adults.

Older adults, especially those with chronic medical and neurological disorders are often 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 with AD. Low light levels and lack of structured social and physical activities in long term care facilities may further decrease the amplitude of circadian rhythms. In fact, lower daytime light levels are associated with an increase in night-time awakenings, even after controlling for the level of dementia [32].

Finally, while there is no direct evidence for a genetic basis for ISWRD, there are several lines of evidence that suggest that the sleep disturbance seen in AD is at least partially based on genetic factors. Actigraphic studies of AD patients have demonstrated longitudinal deterioration of sleep quality, [33,34] and most of this longitudinal variance in sleep appears to be related to an inherent “trait” of the individual patient. This suggests that genetic factors may help determine the ultimate course and level of sleep deterioration seen in a given AD patient [35,36] a hypothesis consistent with considerable research suggesting that much of the circadian variation in many physiological 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 irregular sleep-wake rhythm 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 should also be strongly encouraged [40–43]. A multi-component approach using a variety of behavioral treatment options is recommended.

Light—The overall approach to light therapy for the treatment of the irregular sleep wake type is to increase both the duration and intensity of light exposure throughout the daytime and avoid exposure to bright light in the evening. Bright light exposure delivered for two hours in the morning at 3,000 to 5,000 lux over the course of four weeks has been found to decrease daytime napping and increase nighttime sleep in demented subjects[44]. Light may further help consolidate nighttime sleep, decrease agitated behavior, and result in stronger amplitudes of the circadian rhythm [38,39,44].

Melatonin—When compared to the effects of bright light, studies evaluating the use of melatonin in irregular sleep wake disorder have yielded less consistent results. [24]. Serfaty, M., et al. [45] randomized forty-four participants with DSM-IV diagnosis of dementia and co-morbid sleep disturbance to a seven-week double blind crossover trial of two weeks of slow release melatonin (6mg) versus placebo. It should be noted that only 25 out of 44 patients completed the trial. Melatonin had no effect on actigraphically-measured total time asleep, number of awakenings, or sleep efficiency. Another large scale trial of 157 patients with 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

towards improvement was seen with 10 mg. Overall, the efficacy of melatonin treatment for circadian and sleep disorders remains undetermined (for review see: Brzezinski et al. [47]).

However, some success has been shown in small studies in using melatonin to treat sleep disturbances in children with psychomotor retardation and presumed ISWR [48]. Significant, although incomplete benefit was also reported in an open label trial of melatonin 2 to 20 mg given at bedtime to children with varied neurological disabilities with 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 et al. [52] documented that elderly subjects reported decreased daytime sleep and increased participation in social and physical activities and social conversation by following a routine of reduced time in bed during the day, structured bedtime routine at night, 30 minutes or more of sunlight exposure a day and increased physical activity.

The use of a multi-modal non-pharmacological 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 RCT testing such an approach was recently conducted in a group of community dwelling AD patients, with inferred ISWRD diagnoses [53]. Thirty-six community-dwelling (AD) patients 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 were also instructed to walk daily and increase daytime light exposure with the use of a light box. Control subjects received general dementia education and caregiver support. Sleep was measured actigraphically. Active treatment patients showed significant reductions in number of nighttime awakenings and total time awake at night compared to control subjects. At 6-month follow-up, treatment gains were maintained and additional significant improvements in duration of night awakenings and circadian organization of sleep emerged.

The most effective ISWRD treatments appear to require a combination of structured social and physical activity, exposure to light during the day, along with minimizing nighttime light and noise[39,51,54,55]. However, a more recent study showed that light alone did not improve nocturnal sleep, but that a combination of light and melatonin (5 mg) increased daytime wake time and activity levels and also strengthened the rest-activity rhythm in patients with AD [56]. Riemersma-van der Lek et al found that bright light exposure during the day had a modest benefit in improving cognitive function and mood, whereas, melatonin 2.5 mg taken in the evening, shortened sleep latency and increased sleep duration, but adversely affected mood in elderly residents of group care facilities[57]. 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.

Conclusions

Individuals with ISWRD often present with symptoms of sleep maintenance insomnia and excessive daytime sleepiness. ISWR should always be considered in the differential diagnosis

of sleep disturbances in older adults and children with neurological 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 and wake rhythm of ISWRD. Studies of the effectiveness of pharmacologic treatments for ISWRD have generally yielded negative or inconsistent results. One exception may be in children with 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 (improve sleep hygiene; decrease nocturnal light and noise levels) and enhance daytime alertness (increase daytime light exposure; increase social and physical activity) is the mainstay treatment for ISWRD. Treatment success for this condition is highly variable and requires tailoring to individual needs. It is expected that rapid advances in our understanding of the genetic regulation of circadian rhythms will better define genetic vulnerability for ISWRD, which should lead to prevention and improved treatment of this circadian-based disorder.

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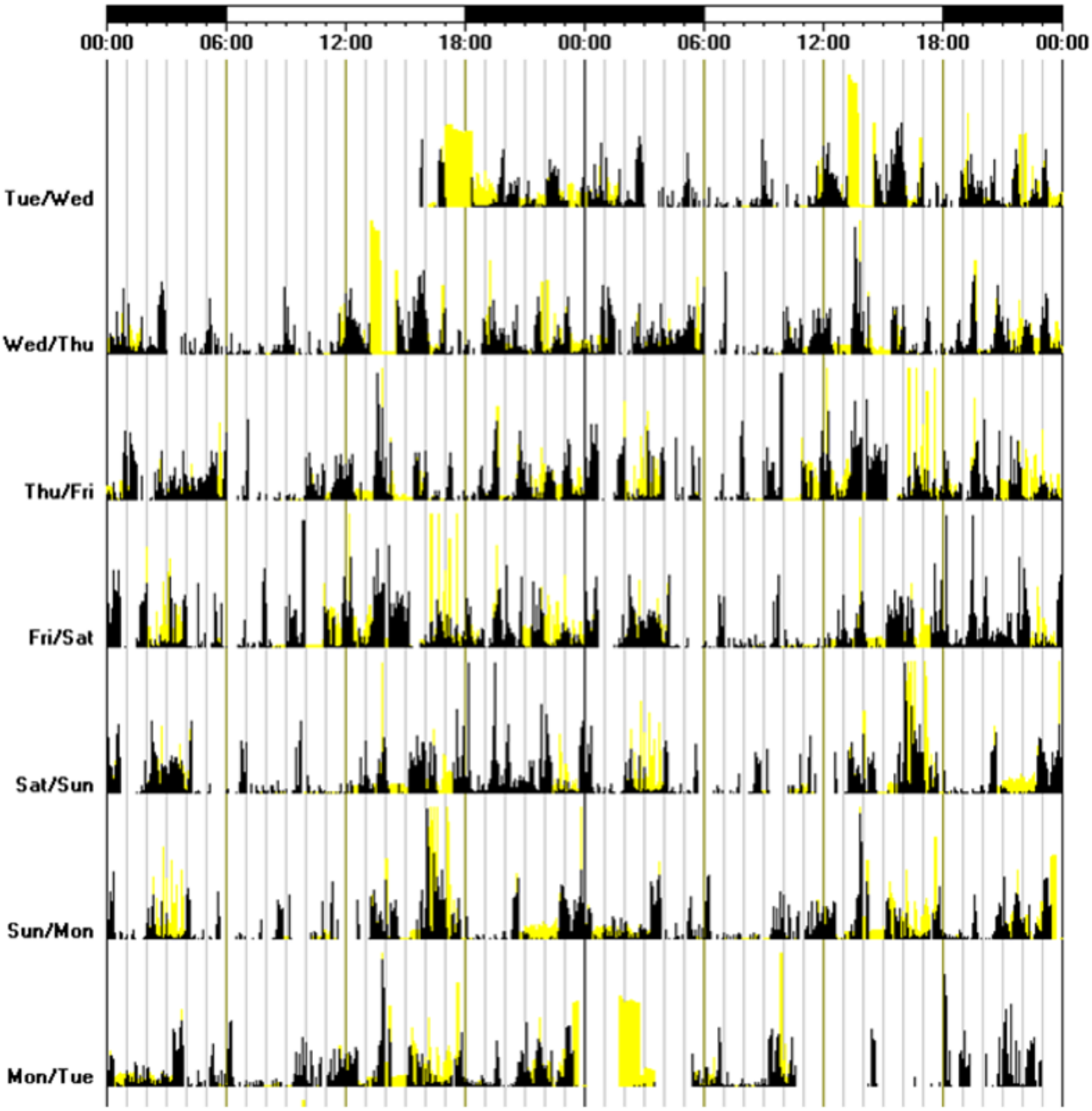

Figure 1.
Actogram obtained by actigraphy over a 7 day period from an older adult patient with ISWRD. The yellow bars indicate timing and level of ambient light exposure and the black bars indicate activity levels recorded at the non-dominant wrist. Note the lack of a discernible circadian sleep and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