Behavioral Presentations of Circadian Rhythm Sleep Disorders

14

Amit Green and Yaron Dagan

Abstract

Circadian rhythm sleep disorders (CRSD) are a group of sleep disorders characterized by a de-synchronization between a person's biological clock and the environmental 24-h schedule. There are six main types of CRSD, namely, advanced sleep phase syndrome (ASPD), delayed sleep phase disorder (DSPD), irregular sleep-wake rhythm (ISWR), free running disorder (FRD), shift work type (SWD), and jet lag disorder (JLD). Physiological data and genetic studies in patients with CRSDs suggest that these disorders result from abnormal functioning of the circadian rhythm system. The diagnosis of CRSD is based on clinical interview and sleep log diaries and/or actigraphic monitoring under a free condition schedule. Bright-light therapy and melatonin administration have proved to be the most effective treatments for CRSD. Difficulties in daytime functioning are one of the prominent characteristics of CRSDs. Individuals with CRSDs frequently fail to adjust to the normal accepted hours of activity. It is common that the daytime functional difficulties that accompany CRSDs are misinterpreted as symptoms of psychopathology or daily dysfunction. CRSDs are underrecognized and frequently misdiagnosed, and therefore treated as psychological, psychiatric, and/or sleep disorders. Recognition and awareness of the characterization of these disorders should improve the diagnosis and treatment of these patients.

A. Green (✉) · Y. Dagan
The Sleep and Fatigue Institute, Assuta Medical Center, Tel Aviv, Israel

The Research Institute of Applied Chronobiology, The Academic College of Tel-Hai, Tel Hai, Israel
e-mail: amitg@assuta.co.il; yaronda@assuta.co.il

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14.1 Introduction

Humans need to adjust their behavior and physiological processes to the conditions of a 24-h day-night (light-dark) period. Synchronization of the endogenous clock with environmental conditions enables the rhythmic changes of behavior and physiological processes to be in phase with the external world. The synchronizing factors are clear environmental cues (so-called time givers—"zeitgebers"), the most prominent of which to the central clock in the SCN is light. Alternating periods of light and dark, day and night, are cues that enforce the period of activity and sleep.

Sleep is regulated by two main factors [1]: the model posits that a homeostatic process (Process S) interacts with a process controlled by the circadian pacemaker (Process C), with time-courses derived from physiological and behavioral variables—the homeostatic pressure and the circadian timing—and the interaction between them. The homeostatic pressure to sleep accumulates as long as a person is awake and therefore the pressure to sleep increases in a positive correlation with the awake time. The circadian factor plays a role in the timing of the sleep; this means that there is a time of day that the probability to fall asleep is higher, for example, in the afternoon between 1 and 4 p.m. and at night between 0 and 4 a.m. The interaction between these two factors will determine the timing and length of sleep [1].

Circadian rhythm sleep disorders (CRSDs) are a group of sleep disorders characterized by an asynchronization between a person's biological clock and the environmental 24-h schedule. These disorders can lead to harmful psychological and functional difficulties and are often misdiagnosed and incorrectly treated due to the fact that physicians are unaware of their existence. In the current chapter we describe the characteristics of CRSDs, its diagnosis and treatment, as well as the relationship to daily dysfunction and disabilities.

The timing and length of sleep display large interindividual differences in human behavior. Sleep and wake times show a near-Gaussian distribution in a given population, with extreme early types (larks) waking up when extreme late types (owls) fall asleep. This distribution is predominantly based on differences in an individual's circadian clock. Circadian rhythm sleep disorders (CRSDs) are caused by disruption of the synchronization of the endogenous circadian rhythm system and the external 24 h of the dark-light period of the earth. Almost by definition, a CRSD involves an abnormality in the timing of sleep relative to the conventional circadian phase for sleep.

Six distinct CRSDs were characterized and are currently recognized in the International Classification of Sleep Disorders (ICSD-3) [2]: delayed sleep-wake phase disorder (DSPD), advanced sleep-wake phase disorder (ASPD), irregular sleep-wake phase type (ISWR), non-24 h sleep-wake rhythm disorder, jet lag type (JLD), and shift-work type (SWD) [2]. The prevalence of CRSDs is unknown;

although if we take into account the enormous number of people who do shift-work or fly, it must be high. There are very limited community-based epidemiological studies of CRSDs [3, 4]. A clinical experience review regarding the proportion of CRSDs by Dagan and Eisenstein [5] found that DSWPD was the most common CRSD diagnosis, followed by non-24 h sleep-wake rhythm disorder; on the other hand, ASWPD and ISWR were very rarely diagnosed, accounting for less than 2% of the CRSD patients.

14.2 Assessment and Measurements of CRSD

14.2.1 Sleep Logs/Diaries

The sleep-wake cycle is a rough indicator of circadian phase, but it is strongly influenced by homeostatic sleep drive, as well as many other factors that make unclear or "mask" the underlying circadian signal. Sleep logs/sleep-wake diaries are consistently recommended as a method for evaluating sleep schedules in CRSD patients; however, there are no widely accepted, standardized sleep logs, and investigators and clinicians often construct their own. Sleep logs have apparent face validity and can provide data on qualitative as well as quantitative aspects of sleep. Although they are commonly used in sleep clinics, the reliability or validity of sleep logs and sleep diaries has not been tested as a clinical assessment tool for CRSDs.

14.2.2 Actigraphy-Watch Monitoring

The common and standard biological method for assessing the circadian rhythm is to assess the rhythm of rest and activity, using an actigraphy watch. Actigraphy monitoring is the recommended and the best manner for assessing CRSD; sleep polysomnography is not applicable to assess CRSD. The measurement is done with a small watch-like device that is equipped with motion and light sensors and is usually placed on the wrist of the nondominant hand. In general, the actigraphy and sleep diaries/logs are collectively used in the diagnosis of CRSD because they allow measuring sleep in both an objective and a subjective manner. Several studies have demonstrated that human wrist activity often shows a robust circadian pattern. Morgenthaler et al. [3] reported that the circadian period of the actigraph-defined sleep/wake rhythm accurately predicted the period of the PSG-defined sleep/wake rhythm, measured simultaneously. Actigraphy provides an accurate estimation of the sleep and wakefulness cycle that can be readily obtained over multiple sleep cycles and is thus very useful for the longitudinal assessment of sleep patterns or rhythm disturbances. The use of actigraphy for evaluation of sleep and wake cycles is a common practice in sleep labs when there is a need for an objective way to assess CRSD. In practice, actigraphy monitoring should be performed for a period of 1 week (at a minimum) to 2 weeks, in "free condition"—the patient is free to go

to sleep and wake up according to his own choice without any obligation (e.g., work, study).

14.2.3 Questionnaire

The "Morningness-Eveningness Questionnaire" (MEQ), developed by Horne and Ostberg in 1976, aimed to determine when the respondent's natural tendency to be active lies during the daily temporal span [6]. The MEQ has become a widely used instrument to classify circadian tendencies in studies of normal subjects as well as patients. The MEQ score is often assumed to be correlated with core parameters of human circadian organization such as the timing of sleep [7, 8] and possibly an endogenous circadian period [9]. Another questionnaire, the Munich Chronotype Questionnaire (MCQ), was developed to assess morning and evening preferences [10, 11].

For research and not clinical needs, circadian rhythms can be quantitatively estimated by the measurement of the clock-controlled physiological processes. Such measurements include the onset of melatonin secretion in the dark (dim light melatonin onset—DLMO), daily changes in the concentration of 6-sulphatoxymelatonin (6-SMT) in the urine, and the circadian rhythm of core body temperature.

14.2.4 Patient's Medical History by Physicians

Patients need to be asked about the chief circadian sleep wake symptom: time onset of routine activity in the patient's daily life (wake time, daily activities, daytime napping habit, activities before sleep, time to go to bed, activities in bed before falling asleep, and sleep description), alertness during the day, timing of hunger and eating habits, timing of best cognitive performance, preferred sleeping time during vacation in order to assess the natural sleeping time, family history with sleep and CRSD disturbance, and type and amount of drugs and alcohol consumption during the day. Patients are suggested to keep a sleep diary or sleep logs for a 1- to 2-week period.

In sum, the best method to make the diagnosis of CRSD is by a clinical interview and 1-2 weeks of actigraphy monitoring or sleep log in free schedule conditions.

14.3 Risk Factors of CRSD

14.3.1 Head Trauma

Minor traumatic brain injury (mTBI) might contribute to the emergence of circadian rhythm sleep disorders. One-third of the patients with complaints of insomnia following mTBI were diagnosed with CRSD of DSWPD and IRSWD types.

14.3.2 Age

Although there are few reports that ASWPD is associated with older age and DSWPD is associated with the age of adolescence, we did not find that age is a risk factor for CRSD. We may suggest that the circadian system endures some changes over the course of the life cycle.

14.3.3 Gender

We found no evidence suggesting any gender differences in CRSD, or that gender might be a risk factor for CRSD per se.

14.3.4 Drugs Side-Effect

Several studies found that administration of antipsychotic drugs such as haloperidol or fluvoxamine can induce CRSD such as DSWPD [12, 13].

14.3.5 Exposure to Artificial Light at Night (ALAN)

Negative physiological outcomes due to exposure to artificial light at night (ALAN) have been a focus of research in the last two decades. Results of studies in recent years show a wide range of ALAN effects, arising from indoor and outdoor lighting, on the human biological clock. Such effects include pineal melatonin suppression, changes in body temperature regulation, and development of circadian and other sleep disorders [14–20]. Modern living styles characterized by nocturnal living patterns, shift-time work, and working in offices with little variation in illumination throughout the day and night may also induce disorders in biological rhythm. Moreover, in recent years several studies found that exposure to ALAN illumination from digital media devices can disrupt circadian rhythm. Green et al. [21, 22] report that exposure to illumination prior to bedtime interfered with markers of human chronobiology known to play a role in sleep regulation. We noted that ALAN from digital media devices suppressed both secretion of melatonin and normative thermoregulation. Therefore, continuous exposure to nighttime illumination from digital media devices may be a risk factor to developing sleep or sleep/wake circadian disorders. It is well-established in the sleep literature that targeted exposure to bright ALAN can delay sleep onset and melatonin secretion [14–16, 23, 24], and therefore is considered an effective treatment for circadian rhythms sleep disorders [25, 26]. In our opinion, extended exposure to light from digital screens at night is in practice a form of unintended “light therapy” that affects the circadian clock and its derivatives and consequently influences sleep capacity and quality.

14.4 Advanced Sleep Wake Phase Disorder (ASWPD)

Advanced sleep phase disorder (ASWPD) is characterized and defined by a stable sleep schedule that is several hours earlier than the conventional or desired time. There is no standard for how much earlier a sleep schedule needs to be in order to qualify as pathological. Diagnosis depends on the amount of discomfort the patient expresses about being unable to adapt to a more conventional sleep schedule after ruling out other causes of sleep maintenance insomnia. The prevalence of ASWPD is about 1–2% and ASWPD is thought to be much less common than DSPD, but because an early sleep pattern results in fewer social conflicts the incidence may be underestimated. The mechanisms leading to this condition are unknown, but hypotheses have usually been the opposite of those thought to underlie DSWPD.

Diagnosis of ASWPD is characterized by an advance in the phase of the major sleep period in relation to the desired sleep and wake times; individuals with this condition would be predicted to score as morning types (M-type) with high values on the MEQ. Several studies report ASWPD patients scored high on the MEQ indicating morning-lark traits [27–29]. Age is associated with increased ASWPD with age; several studies using the MEQ questionnaire found that age was associated with morningness type of sleep-awake schedule (M-type) [30, 31]. There are no gender differences associated with ASWPD according to available data.

A few years ago, a young girl (age 11) was referred to our sleep clinic. Her mother described an unusual sleep-wake schedule; according to the mother's description, the girl sleeps once she comes home from school until the middle of the night. An actigraphy recording for a week, in free-schedule condition, showed that the girl is falling asleep at 3–4 p.m. and waking up at 1–2 a.m. This type of ASWPD is very extreme, leading to social isolation and psychological distress since her ASWPD does not leave this young girl any free time, or time for social interaction with her friends in addition to long hours alone and awake at night. Since treatment of ASWPD includes bright light therapy given as close to sleep time as possible, this might delay sleep onset. In addition, melatonin should be taken in the morning. We prescribed treatment of light therapy with a light box during the afternoon (4–5 p.m.) and melatonin administration in the morning (Fig. 14.1).

14.5 Delayed Sleep Wake Phase Disorder (DSWPD)

Delayed sleep phase disorder (DSPD) is characterized by a stable sleep schedule that begins substantially later than the conventional or desired time (2–4 a.m.), and by the inability to fall asleep and awaken at a desired time, leading to significantly later sleep onset and wake times (10 a.m.–12 p.m.). The first description of the disorder was by Weitzman and colleagues [32]. The pathophysiology of DSWPD is attributed to longer τ (see Chap. 3), misaligned phase relationship between endogenous clock and sleep-wake cycles, reduced photic entrainment, and/or altered sleep homeostasis. Patients suffering from DSWPD are often required to rise early in the morning in order to adhere to domestic, school, or job obligations. Due to late sleep

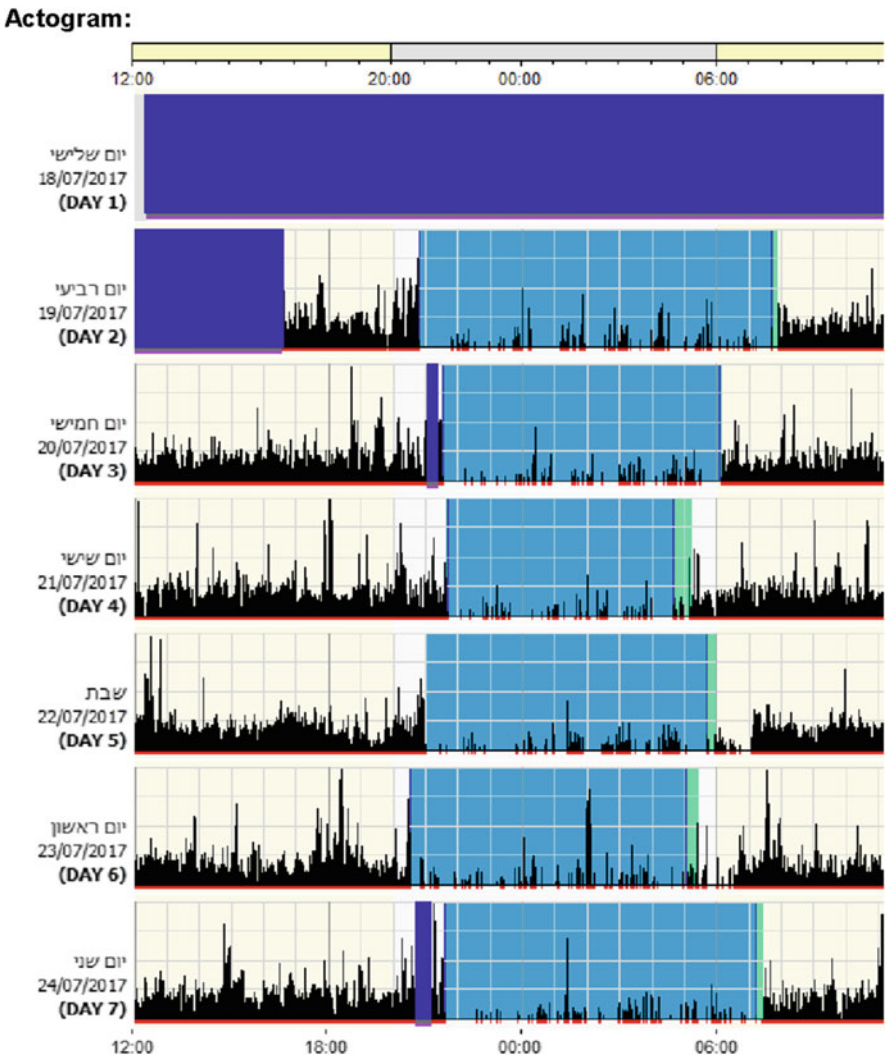

Fig. 14.1 Actigraphy recording of advanced sleep wake phase disorder (ASWPD) patient

onset, chronic sleep loss is, therefore, a common consequence. DSWPD has been shown to have high comorbidity with other conditions, such as depression, hypochondria, and personality disorders [33]. Patients with DSWPD have sleep onset insomnia and extreme difficulty arising when they attempt to conform to a conventional work schedule or other social demands. A tendency for a delayed sleep schedule is very common during teenage years; nevertheless, this seems to be an outcome of social interaction rather than physiological trait. Psychophysiological insomnia must be ruled out as a cause for the sleep onset insomnia characteristic of DSWPD. Weitzman et al. [32] proposed that a significant number of patients with

sleep onset insomnia may have underlying DSWPD, but this hypothesis has not been systematically pursued. We tend to agree with Weitzman et al.'s [32] claim that since both disorders, DSWPD and insomnia, exhibit prolonged sleep onset, some clinician's may misdiagnosis DSWPD as insomnia. The differential diagnosis between DSWPD and insomnia is important for precise therapeutic intervention, since Insomnia should be treated with psychological treatment such as CBT-I or hypnotic treatment, while DSWPD is conventionally treated with melatonin and light therapy. The etiology of DSWPD is unknown, and it is unclear whether this is a manifestation of intrinsic pathology or a socially reinforced sleep-wake schedule that can be readily modified if circumstances require it. There is solid evidence that melatonin administered 2 h before the desired sleep time to promote a corrective phase advance is an effective treatment for DSWPD. Light therapy with bright light in the morning at close to waking appears to be a reasonable and effective intervention for DSWPD (Fig. 14.2).

14.6 Irregular Sleep-Wake Rhythm (ISWR)

Irregular sleep-wake rhythm (ISWR) is characterized by the relative absence of a circadian pattern to the sleep-wake cycle. Total sleep time may be comparatively normal, but instead of being consolidated into a distinct bout or bouts, sleep times are shortened, and in extreme cases, almost randomly distributed throughout the day and night. ISWR is commonly associated with neurological impairment, such as mental retardation in children and dementia in older adults. The cause (or more likely, the causes) of this association are unknown, but damage to the circadian pacemaker in the suprachiasmatic nucleus (SCN) is clearly implicated as an important, if not a major, etiological factor.

A 47-year-old male was admitted to the Institute for Fatigue and Sleep Medicine complaining of severe fatigue and daytime sleepiness. He described a gradual evolvement of an irregular sleep-wake pattern within the past 20 years, causing marked distress and severe impairment of daily functioning. A 10-day actigraphy record revealed an ISWR pattern with extensive day-to-day variability in sleep onset time and sleep duration. In addition, melatonin level and oral temperature showed abnormal patterns. A further investigation of the patient's daily habits and environmental conditions revealed two important facts. First, his occupation required work under a daylight intensity lamp (professional diamond-grading equipment of more than 8000 lux), and second, since the patient tended to work late, the exposure to bright light occurred mostly at night. To recover his circadian rhythmicity and stabilize his sleep-wake pattern, we recommended combined treatment consisting of evening melatonin administration combined with morning (09:00) bright light therapy (8000 lux for 1 h), plus the avoidance of bright light in the evening. A follow-up 10-day actigraphy monitoring done 1 month after initiating the combined treatment protocol revealed stabilization of the sleep-wake pattern with advancement of sleep phase. In addition, the patient reported profound improvement in maintaining wakefulness during the day. This case study shows that chronic

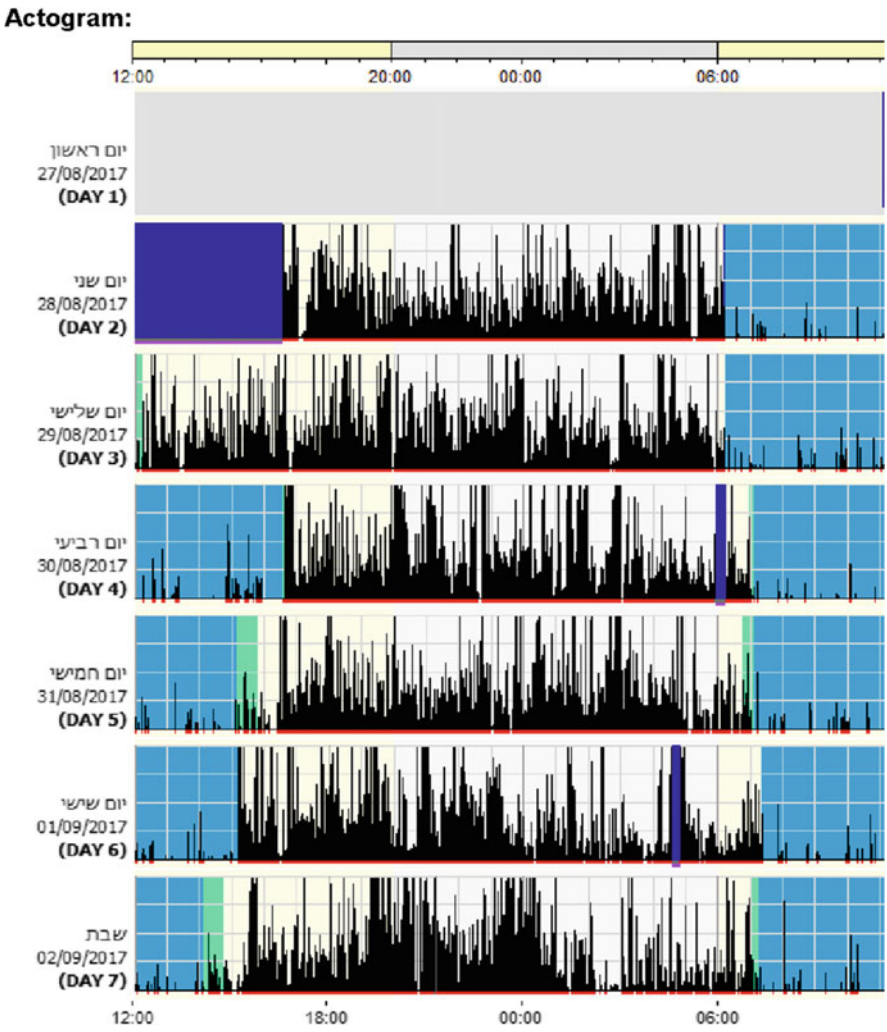

Fig. 14.2 Actigraphy recording of DSPD patient

exposure to bright light at the wrong biological time, during the nighttime, may have serious effects on the circadian sleep-wake patterns and circadian time structure. Therefore, night bright light exposure must be considered to be a risk factor of previously unrecognized occupational diseases of altered circadian time structure manifested as irregularity of the 24-h sleep-wake cycle and melancholy (Fig. 14.3).

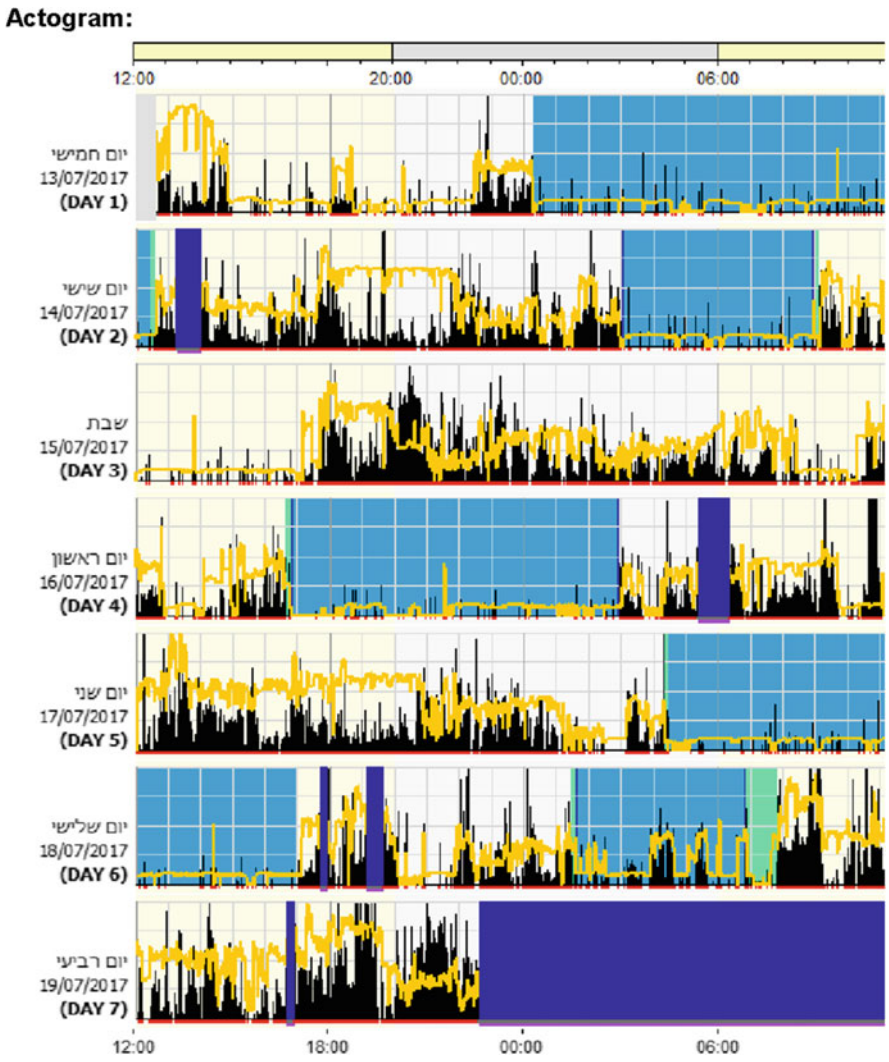

Fig. 14.3 Actigraphy recording of patient with irregular sleep-wake rhythm (ISWR) disorder

14.7 Non-24 h Sleep Wake Rhythm Disorder (NSWRD)

The human circadian period is usually longer than 24 h; the earliest studies of human subjects in free environments concluded that most people have an intrinsic circadian period longer than 24 h, averaging about 24.2 h [34]. Patients with free-running rhythms have circadian cycles that mimic those of subjects in time-free environments, and thus are thought to reflect a failure of entrainment. The condition

is very rare in normally sighted people, but quite common in the totally blind who have no access to the entraining effects of the light/dark cycle [35]. Roughly one-fourth of sighted individuals with NSWRD have related psychiatric diagnoses. Appropriately timed melatonin doses from 0.5 to 10 mg have been shown to entrain totally blind people who have NSWRD.

Dagan and Ayalon [36] reported about a 14-year-old male suffering from significant academic and personal difficulties, who had been diagnosed with depression, schizotypal personality disorder, and learning disabilities. Because of excessive sleepiness, assessment for a potential sleep disorder was performed. An overnight polysomnographic study revealed no primary sleep disorders. Wrist actigraphy revealed an NSWRD (non-24-h sleep-wake pattern). Delay in temperature rhythm and dissociation from melatonin rhythms were also noted. Treatment with oral melatonin restored normal sleep-wake schedule. In a follow-up psychiatric evaluation, none of the above diagnoses were present. This case, from our point of view, is an excellent example how the difficulties to adjust the normal requirements of the society, being awake and active during daylight hours and to sleep during night time, is problematic for CRSD patients in general, and in this case for this young boy with NSWRD. These difficulties in adjusting to the social norm may be misdiagnosed by physicians and psychologists as a psychiatric and/or psychologic disorder and leads to not suitable treatment (Fig. 14.4).

14.8 Shift Work Disorder (SWD)

Shift work refers to nontypical work schedules, including permanent or intermittent night work, early morning work, and rotating schedules. Shift work has become a common practice in the modern Western world and it is estimated that about 15–20% of the workers are working shift-work schedules. There is common agreement that shift-work is associated with a number of health problems, for example, poor sleep, gastrointestinal disorders, abnormal metabolic responses, and increased risk of accidents. Disturbed sleep is perhaps the most dramatic and dominant result of shift-work. A number of survey studies have shown that shift workers have sleep complaints, mainly maintaining sleep after the night shift and initiating sleep before the morning shift [37, 38]. The major effect on sleep architecture is reduced stage 2 and rapid-eye movement (REM) sleep with minor effect on slow wave sleep (SWS). In addition, sleep latency is positively associated with morning shift and is shortened after night shift. Several studies have reported that shift workers report more sleepiness and fatigue than do daytime workers [39, 40]. As with sleepiness, the main reason for night shift deterioration in performance is circadian rhythmicity and sleep loss [41, 42]. Several studies showed decreased performance in parameters of capacity, accuracy, and quality of workers during the night shift [43–45]. In sum, several lines of evidence suggest that rotating shift work might directly or indirectly contribute to decrements in cognitive function.

A long-term risk of major disease such as heart disease and cancer are beginning to be appreciated. Recently, rotating night shifts have been linked to adverse health

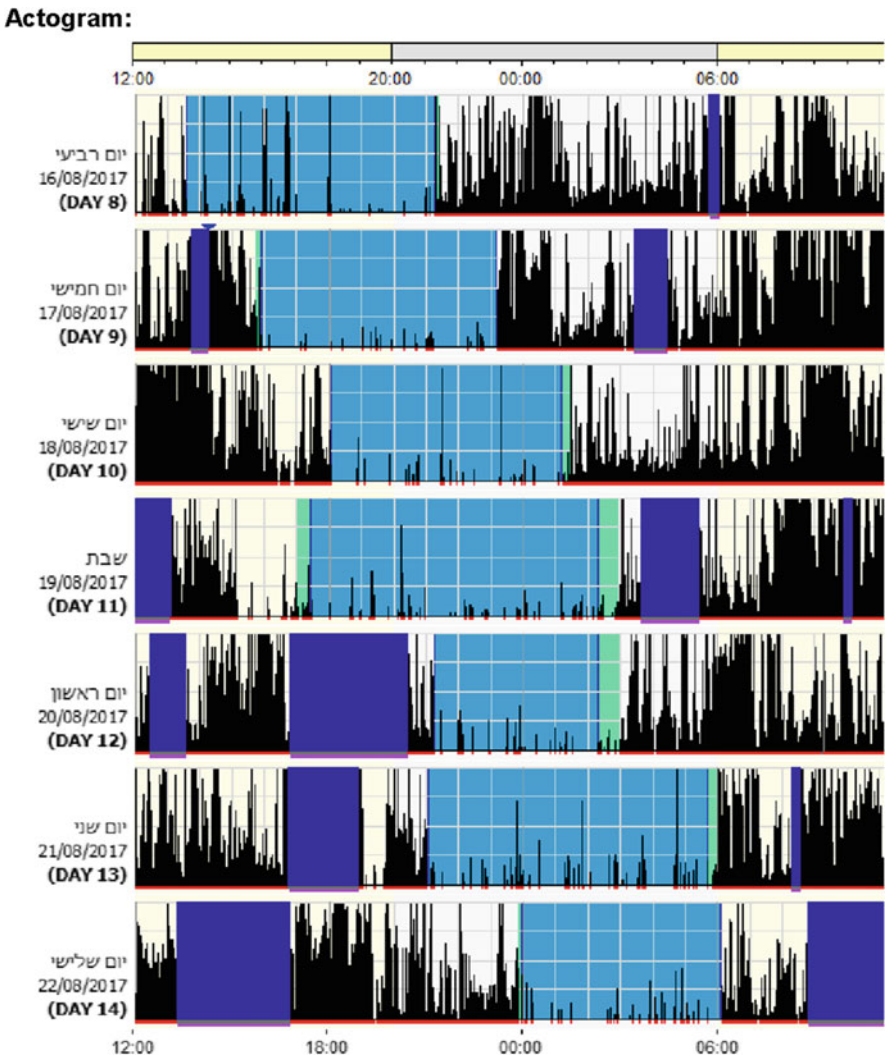

Fig. 14.4 Actigraphy recording of patient with non-24 h sleep wake rhythm disorder (NSWRD)

outcomes, including obesity, type 2 diabetes, and cardiovascular disease [46]. Moreover, Koller [47] noted that reduced health appeared to be earlier among shift workers than among day workers, reflecting the effect of long-term stress due to shift work hours.

Several factors influence the adjustment to shift work. One such factor is the direction of rotation of the shift schedule. A previous study reports that phase delay is easier to accomplish than phase advance [48]. In addition, the length of the work shift is another parameter that influences sleepiness and performance. Moreover, apparently, a rotating shift work schedule causes greater disturbance to the

individual than does an unchanging work schedule. The trait of morningness (the propensity toward preferring morning sleep-wake) has frequently been associated with poor adjustment to shift work [41, 44]. This has also been the case for the trait of sleep rigidity [49]. Finally, inappropriate light exposure during night shifts, which can disrupt circadian rhythm, might adversely affect shift workers' health and performance [50, 51].

14.9 Jet Lag Disorder (JLD)

Jet lag disorder (JLD) is a transient circadian rhythm disorder related to travel across time zones in which there is a discrepancy between the timing of the sleep and wake cycles generated by the endogenous circadian clock and the environmental clock (day-night) in the new time zone. Jet lag results from the new time zone of a biological clock unadjusted to the environmental clock. This absence of rapid adjustment results in loss of sleep at night, and all the daily (circadian) rhythms that are controlled by the body clock are inappropriately phased.

Why does it happen? A recorded rhythm can be regarded as a mixture of components because of effects of the body clock (the endogenous component) coupled with effects of the individual's environment and lifestyle (the exogenous component). These components are usually synchronized, but this synchronicity is lost in the days after a time-zone transition, since, unlike the exogenous component, the endogenous component has not adjusted. Therefore, explicit circadian rhythms will adjust to time-zone transitions at different rates. Those with a larger exogenous component, for example, food intake and physical activity, will seem to adjust more rapidly than those with a larger endogenous component, for example, sleep, mood, and mental performance.

When several (usually three or more) time zones are crossed, JLD is noticed. The subjective symptoms of JLD usually occur within 1-2 days after travel and include a complaint of insomnia or excessive daytime sleepiness and may also include general malaise, somatic symptoms, or other impairments of daytime function. The severity of JLD increases with the number of time zones crossed in flight. In addition, JLD severity of symptoms is positively associated with age for older travelers. Travelers with rigid sleeping habits had more symptoms of JLD than did those with less rigid sleeping habits. Moreover, the incidence and severity of JLD symptoms depends on the direction of the time-zone transition—flights to the east are associated with more JLD than flights westward. JLD symptoms include poor sleep during the new night-time, including delayed sleep onset (after eastward flights); early awakening (after westward flights); fractionated sleep (after flights in either direction); poor performance during the new daytime at both physical and mental tasks; negative subjective changes, which include increased fatigue, frequency of headaches and irritability, and decreased ability to concentrate; gastrointestinal disturbances (indigestion, the frequency of defecation, and the consistency of the stools); and decreased interest in, and enjoyment of, meals.

The best way to lighten JLD is by adjustment of the body clock. The main zeitgebers in individuals are the light-dark cycle and the nocturnal secretion of melatonin. Sleep, physical activity, and food intake have also been implicated. The effects of light exposure and melatonin secretion act to synchronize the body clock with the sleep-wake and light-dark cycles.

Treatments for JLD include: (1) The combination of morning exposure to bright light and shifting the sleep schedule 1 h earlier each day for 3 days prior to eastward travel may lessen symptoms of JLD. (2) Melatonin administered at the appropriate time is indicated to reduce symptoms of JLD and improve sleep following travel across multiple time zones. (3) Short-term use of a sleeping hypnotic is optional for the treatment of jet lag-induced insomnia.

14.10 Types of Treatment for CRSD

14.10.1 Light Therapy

Light therapy is a treatment method in which the therapeutic effect results from exposure to bright light. It is considered the method of choice for the treatment of seasonal affective disorder (SAD) and is often used to treat circadian rhythm disorders. It has been well-established that the solar light-dark cycle is the primary environmental time cue for synchronizing the circadian system of most living plants and animals to the 24-h day. Light/dark cycles are the most common zeitgebers (time keepers) for terrestrial animals, and play an important role in the entrainment of the circadian clock within the SCN. External light cues are transmitted via retinal non-image-forming photoreceptors to the SCN via the retinohypothalamic tract [52, 53].

One of the major functions of the SCN is to regulate the production and secretion of the circadian neurohormone melatonin (MLT) by the pineal gland. MLT production is inhibited by light during the day and facilitated during darkness at night, so that the majority of melatonin secretion takes place in the hours of darkness [14]. In synchrony with MLT secretion is the circadian core body temperature (CBT) rhythm, which peaks in the afternoon, gradually declines in the time for sleep at night, and remains low until the early morning hours. CBT has also been shown to be regulated via transmission of nonvisual information to the anterior hypothalamus by means of preoptic nerves [54, 55]. In sum, light/dark cycles seem to play an important role in relaying external information to the SCN, thereby synchronizing a range of circadian rhythms to each other and the external environment.

The light exposure schedule, intensity, and wavelength, and history of light exposure affect the size and direction of the phase shift of the circadian rhythm caused by exposure to light. Exposure to bright light in the morning causes an advance in the circadian rhythm. In contrast, exposure to bright light in the evening or at night will lead to delay in the circadian phase. In sum, bright light just after waking up, and/or in the last 2 h of the sleep period, causes a circadian phase advance, while the light therapy exposure in the evening/nighttime will cause a circadian phase delay. Another major factor for the success of the light therapy is the

duration and intensity of the light. In practice, with lamps with light intensity of 2500 lux, the recommended exposure duration is generally 2 h, while for those with light intensity of 5000–10,000 lux, 30 min of exposure is sufficient. In clinical practice, patients might not routinely follow instructions as precisely as prescribed. Therefore, the effectiveness of light therapy in clinical practice is usually lower than that observed in empirical studies. The circadian clock is very sensitive to short wavelength; it has been demonstrated that the retinal photoreceptors involved in the regulation of the circadian rhythm containing melanopsin are most sensitive to blue light with a wavelength of 480 nm. Several studies found that exposure to light in short wavelengths (460–480 nm) can affect circadian phase and sleep. It is also important to explain in what part of a 24-h period one should avoid artificial light, especially that emitted by computer screens, TV screens, tablets, and smartphones [56]. DSWPD patients should not use such devices 2 h before their usual bedtime, and not stay in brightly lighted rooms as well. Conversely, patients with ASWPD should not be exposed to artificial light from digital media screens after awakening at night, because it may result in further phase advance of their sleep-wake rhythm [22, 56].

14.10.2 Melatonin Treatment

A variety of doses of melatonin have been given to subjects for phase shifting. The threshold for a chronobiological effect occurs at physiological blood levels (about or below 50 pg/mL). The common doses for treatment of CRSD are usually between 3 and 5 mg/day. Recent studies suggest that timing of taking the pills is more important than the dose itself [57]. There may be some synergistic effect when light and melatonin are used to promote shifts in the same direction. Studies on biological markers implicated in circadian rhythms have established the optimal timing of melatonin and/or light therapy administration. These studies [58, 59] showed that the largest phase shift occurs when melatonin and light therapy are applied in concordance with DLMO occurrence and a core body temperature minimum. Revell and her colleagues [60] demonstrated that a combination of a gradual advancement of the sleep schedule (wake time 1 h earlier each morning) combined with bright light upon awakening and melatonin (0.5 or 5 mg) in the afternoon, induced a maximal phase advance while maintaining circadian alignment, suggesting a synergistic effect of the treatments. In sum, the robust phase advance occurs when melatonin is administered at least 10 h before a usual time of getting up and light therapy is used during the last 2 h of the usual sleep period. The strongest phase delay occurs when melatonin is administered in the last 2 h of the usual sleep period and light therapy is used during the first half of a usual sleep period.

14.11 Psychological, Behavioral, and Cognitive Consequences of CRSD

14.11.1 Psychological and Emotional Aspects

Several studies report that patients having CRSD are at high risk to suffer from psychological distress, mainly since they suffer from difficulty to adjust to general and common hours of activity. DSWPD patients, for example, have been reported to shown high comorbidity with depression, hypochondriasis, and personality disorders [61, 62]. In addition, patients with DSWPD are shown to have an elevated score on the Minnesota Multiphasic Personality Inventory–Second Edition [61, 63]. In one study, the DSWPD group scored higher than the control group on anxiety and depression assessments [64]. Studies have shown a consistent association between eveningness and depressive symptoms and/or depressive disorder [65–68]. Eveningness was associated with an increased risk of depression, even after adjusting for sleep-related factors (Kitamura et al. 2010). Furthermore, eveningness and insomnia were recently found to be independent predictors of non-remission in depressed patients [69]. A study designed to examine whether sleep problems (daytime sleepiness, insomnia, and circadian misalignment) mediate the association between eveningness and negative emotionality found that eveningness was an independent risk factor for negative mood [70]. Similarly, eveningness and subjective sleep quality were independent risk factors for increased depressive symptomatology, and sleep quality failed to explain the link between eveningness and depressive symptoms [71]. Along the same lines, we previously found that the evening type was associated with clinically diagnosed major depression [65]. In addition, Costa and McCrae [72] showed that young adults with DSWPD scored higher on neuroticism and lower on conscientiousness compared to the control group. The neuroticism dimension represents the individual's tendency to experience psychological distress, and most psychiatric conditions yield elevated scores on neuroticism. The low scores on the conscientiousness dimension, according to the authors, may explain the notion that some patients with DSWPD are difficult to treat, noncompliant with light therapy and melatonin administration, and become school or academic dropouts. In a recent study performed by Micic et al. [73], DSWPD and NSWRD patients showed higher neuroticism compared to control, and significantly lower extraversion, conscientiousness, and agreeableness. Conscientiousness was associated with phase timings of circadian rhythms and lifestyle factors within the DSWPD patients. According to the authors, these findings suggest that CSRD may not only stem from circadian abnormalities, but personality factors may also drive lifestyle [73]. A good example of how complicated and tricky the association between CRSD and psychological state might be can be understood by this example: Several years ago, a young boy was referred to our sleep institute from day-care hospitalization of the psychiatric clinic. This 14-year-old male was suffering from significant academic and personal difficulties, had been diagnosed with depression, schizotypal personality disorder, and learning disabilities. Because of excessive sleepiness, assessment for a potential sleep disorder was performed. An overnight

polysomnographic study revealed no primary sleep disorders. Wrist actigraphy revealed a non-24-h sleep-wake pattern. Delay in temperature rhythm and dissociation with melatonin rhythms were also noted. Treatment with oral melatonin restored normal sleep-wake schedule. In a follow-up psychiatric evaluation, none of the above diagnoses were present. Greater awareness of sleep disorders may prevent psychiatric misdiagnosis of treatable sleep-wake schedule disorders. In sum, a major difficulty and challenge facing CRSD patients is their effort to adjust the norms of awake-active during daytime and sleep in the night-time of the society. A failure to do so may lead to mood disorder such as anxiety, depression, and decrease in self-esteem of CRSD patients. In addition, lack of awareness to the symptoms CRSDs among physicians, psychologist, and parents of children with CRSD can cause misdiagnosis of the CRSD. This mistaken diagnosis can lead to fault attribution of the difficulties to motivational and psychological factors instead of the real problem.

14.11.2 Attentional, Memory, and Cognitive Performance

Circadian differences in cognitive performance have been the subject of scientific investigation since 1885, when Ebbinghaus first reported a remarkable effect of the time of day on the efficiency of learning serial lists of nonsense syllables [74]. In general, human cognitive performances are best between 12.00 and 18.00 h, just before body temperature reaches its highest, and worst when temperature was lowest, between 04.00 and 06.00 h. More specifically, performance on cognitively complex tasks, especially those that require verbal reasoning and/or short-term memory, is highest in the morning and steadily declines during the rest of the waking day [75, 76]. Johnson et al. [72] found prominent circadian variations in the mean 24-h patterns of short-term memory, subjective alertness, and calculation performance during the constant routine. The patterns of subjective alertness and cognitive performance paralleled the body temperature cycle and reached their lowest point just after the minimum of temperature. These outcomes became apparent when overall performance on short-term memory tasks in fact paralleled the body temperature cycle [72]. On the other hand, other studies that disassociated the circadian variable found an effect to the sleep/wake factor were noted, meaning that sleep deprivation also affects the cognitive performance. It appears that cognitive performance is influenced by two interacting factors: an endogenous circadian process that is coupled to the temperature cycle, and the sleep/wake-related process.

A major factor on our cognition is the attention dimension. Dagan and Borodkin [77] state that the association between CRSDs and attention deficit disorder (ADD) and attention deficit/hyperactivity disorder (ADHD) should also be revealed. A relatively high prevalence (19.3%) of these disorders was reported in a large sample of patients with CRSDs attending a sleep clinic. In a retrospective study of 45 children and adolescents with DSPS (aged 6–18) who were treated with melatonin, almost half of the sample had a comorbid diagnosis of ADD or ADHD pretreatment.

Gamble et al. [78] conclude that ADHD symptom severity correlates with delayed sleep timing and daytime sleepiness, suggesting that treatment interventions

aimed at advancing circadian phase may improve daytime sleepiness and attention abilities. In addition, ADHD adults with combined hyperactive-impulsive and inattentive symptoms have decreased sleep quality as well as the delayed sleep timing of predominately inattentive subtypes. The understanding that sleep disorder in general, but CRSD specifically, can increase or impair symptoms of ADHD, and that good sleep hygiene improves attention and concentration tasks, has sparked interest in the investigation of possible etiological relationships between sleep disorders and ADHD. Recent studies indicate that one-third of children and two-thirds of adults with ADHD have symptoms of sleep disorders such as daytime sleepiness, insomnia, delayed sleep phase syndrome, and fractured sleep [79]. Treatment of adolescents suffering from DSWPD with melatonin was reported to improve not only the circadian disorder but also their academic performance [80]. A recent study in the Netherlands, conducted to evaluate whether the association between ADHD and Seasonal Affective Disorder was mediated by the circadian rhythm, found that late self-reported sleep onset was an important mediator in the significant relationship between ADHD symptoms and probable SAD, even after correction for confounders. This implies that treating patients with SAD for possible ADHD and delayed sleep onset time may reduce symptom severity in these complex patients [81]. In line with the above, a recent study reports high impulsive individuals displayed phase-delayed patterns of sleep, a decreased total sleep time and sleep efficiency, and disrupted circadian sleep-wake cycle [82]. These outcomes revealed the association between attention deficit hyperactivity disorder symptoms and sleep and circadian rhythm disturbances, and this may be associated with impulsive traits illnesses in which impulsivity is one of the core features of the ADHD disorder. In sum, we find reliable evidence for circadian rhythm disruption in ADHD and this disruption may present a therapeutic target for future ADHD research.

14.11.3 Behavioral and Physical Activity and CRSD

Consider, for example, a patient with DSPS who is expected to come to his workplace by 8 or 9 a.m. In order to fulfill this requirement, this individual is forced to wake up at what might be the middle of his internal night. It is not surprising, therefore, that he will frequently be late and/or absent, a pattern that will most likely subject him to disciplinary actions up to firing. If, however, he manages to meet the attendance standards, his performance will be subject to the detrimental effects of sleep loss and time of day. In childhood and adolescence, when CRSDs usually emerge, the impairment of daytime functioning can be even more remarkable than in adults. Unlike adults, who can at times choose a lifestyle that corresponds to their sleep-wake cycle, the activity hours of persons of younger age are constrained by a strictly predetermined school timetable. The inability to adjust to this timetable may be associated with deteriorated school performance.

Sleep deficiency due to either circadian rhythm sleep disorder or insufficient sleep duration is strongly associated with motor vehicle crashes in the general population, independent of self-reported excessive sleepiness [83, 84]. Patients that suffer from

CRSD tend to have insufficient sleep hours due to their irregular circadian sleep wake disorder. For example, DSPD patients tend to go to sleep late at night and therefore are more vulnerable to suffering from sleep loss. ASWPD patients in contrast tend to go to sleep early and they get sleepy and tired in the early evening. Patients with NSWRD and IRSD tend to have an unusual sleep schedule. All of these can lead to excessive sleepiness during the day and night hours and therefore put CRSD patients at a high risk for work accident and motor vehicle crashes.

There is evidence that many aspects of physical activity display circadian rhythms that are closely in phase with that of core body temperature. These aspects include peak force of muscle contraction, anaerobic power output, performance in long-jump and high-jump, and an individual's motivation to undertake sustained effort. Furthermore, sports that simulate contests or that involve timing skills, for example, swimming, football, and tennis, show circadian variation.

We believe that if we consider any CRSD as discrepancies between the inner-biological clock and the outer-environmental clock, we will expect to find decline and lower abilities and performance when the environmental clock is not in phase with their inner-biological clock. Some examples of human rhythms in disease processes include nighttime asthma, early morning increases in blood pressure, death rate from cardiovascular disease and stroke, and disrupted menstrual cycles. Thus, diagnostic tests should be aware of these rhythms. Measurement of a given rhythmic variable in someone who suffers from CRSD (DSWPD, ASWPD, NSWRD) or has just crossed several time zones (JLD), or worked several night shifts, can give false-negative or false-positive results. This means that if DSWPD patients are evaluated in early morning hours in psychological, behavioral, and cognitive tests, we will expect to find low abilities compared to evening assessment. In contrast, ASWPD patients will show better results in the early morning hours compared to evening-night hours.

14.12 Conclusion

Circadian rhythm sleep disorders (CRSDs) arise when an individual's sleep-wake rhythm does not match the environmental 24-h schedule.

Difficulties in daytime functioning are one of the prominent characteristics of CRSDs. Individuals with CRSDs frequently fail to adjust to the activity hours accepted in most social, occupational, and academic settings, due to incompatibility of their internal biological rhythms with the environmental timetable. Daytime functional difficulties that accompany CRSDs are frequently misinterpreted by parents, teachers, psychologists, and physicians as symptoms of psychopathology or maladaptive behavior. Although these disorders can be relatively easily diagnosed and treated, as mentioned, until now many cases of CRSDs are underrecognized and/or misdiagnosed and wrongly treated as psychiatric disorder, insomnia, maladaptive function due to excessive day somnolence or sleepiness. Consequently, these patients receive inappropriate treatment, such as hypnotics or stimulants, which can enhance the psychological distress and add to the adjustment difficulties

that accompany CRSDs. It is of great importance to raise the awareness of these disorders on the part of pediatricians, physicians, neurologists, psychiatrists, and psychologists.

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