

Circadian rhythm sleep disorders (CRSD)

Yaron Dagan

Institute for Fatigue and Sleep Medicine, “Sheba” Medical Center, Affiliated to “Sackler” Medical School, Tel Aviv University, Israel

KEYWORDS

CRSD, DSPS, ASPS, non-24-h CRSD, melatonin, head trauma, haloperidol, SSRI, fluvoxamin, actigraph, sleep disorders

Summary Circadian Rhythm Sleep Disorders (CRSD) are a group of sleep disorders characterized by a malsynchronization 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 doctors are unaware of their existence. In the following review we describe the characteristics of CRSD, their diagnosis, treatment as well as their relationship to psychopathology, psychotropic drugs and head trauma.

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INTRODUCTION

The inborn human sleep-wake schedule is longer than 24 h. It is synchronized to the external 24-h day, and reacts to environmental zeitgebers (time cues). The environmental zeitgeber – bright light – seems to play the crucial role in this process [1, 2]. The sleep-wake schedule is synchronized also with other circadian cycles in the body: body temperature, and the secretion of: melatonin, growth hormone and cortisol.

Human beings sleep at night and are awake during the day. This essential phenomenon so taken for granted can become chronically impaired in some people leading to a group of disorders called: Circadian Rhythm Sleep Disorders (CRSD) [3, 4]. These disorders are usually unfamiliar to the physician thus frequently misdiagnosed and incorrectly treated. The aim of this review is to shed light on these disorders: characteristics, diagnosis, treatment and applications in medicine.

WHAT ARE CRSD?

Twenty years ago Weitzman *et al.* [5] first described 30 of their insomnia patients (7%) as suffering from Delayed Sleep Phase Syndrome (DSPS). These patients had a tendency to fall asleep very late at night and to experience difficulty rising at a desired time in the morning. They also found that when these patients were allowed to sleep without external restrictions, they slept for a normal length of time and exhibited no pathology in their sleep architecture. Their patients were younger than other types of insomniacs, without differences of sex prevalence, displaying no specific psychiatric disorders, and of various ages of onset. This discovery led to the recognition of the existence of Circadian Rhythm Sleep Disorders (CRSD) other than DSPS.

Today, the criteria for the definition and diagnosis of CRSD (formerly Sleep Wake Schedule Disorders – SWSD) are described by the International Classification of Sleep Disorders (ICSD) [3, 4]. According to this definition, CRSD constitute a misalignment between the patient’s sleep pattern and that, which is desired or regarded as the societal norm. Sleep episodes occur at inappropriate times and as a result, wake periods occur at undesired times, therefore, the patient complains of insomnia

Correspondence should be addressed to: Y. Dagan, Institute for Fatigue and Sleep Medicine, “Sheba” Medical Center, Fax: 972-3-5349368. E-mail: ydagan@post.tau.ac.il

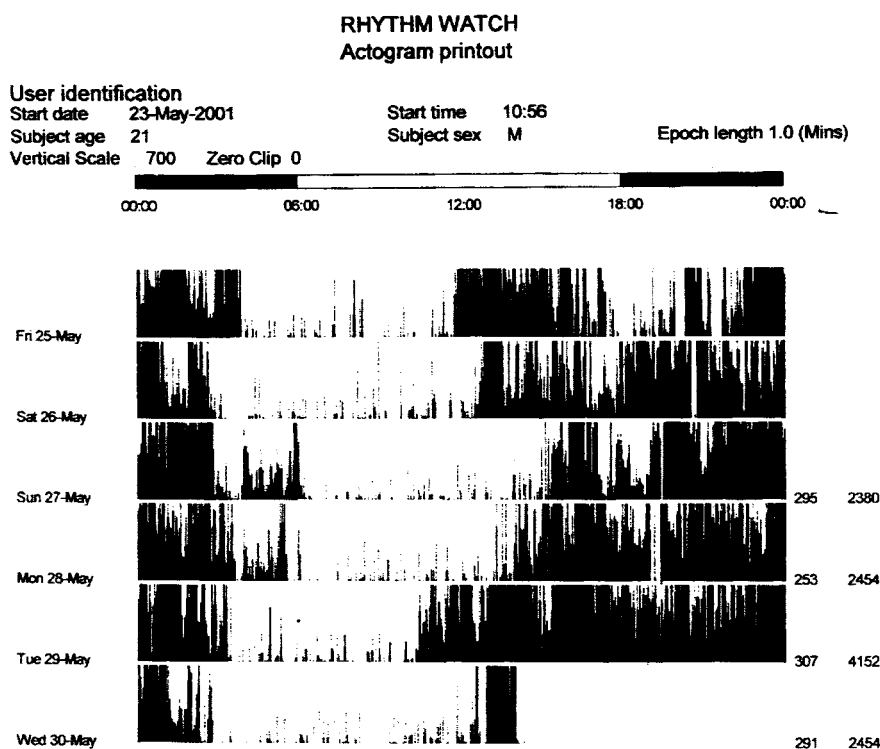


Figure 1 Delayed Sleep Phase Syndrome.

or excessive daytime sleepiness. For most of the CRSD, the major sleep episode is of normal duration with normal REM/NREM cycling, although intermittent sleep episodes may occur in some disorders.

CRSD are divided into six subgroups [3]:

1. Delayed Sleep Phase Syndrome (DSPS): in this disorder the major sleep episode is delayed in relation to the desired clock time resulting in symptoms of sleep-onset insomnia or difficulty in awakening at the desired time (Fig. 1).
2. Advanced Sleep Phase Syndrome (ASPS): the major sleep episode is advanced in relation to the desired clock time, resulting in symptoms of compelling evening sleepiness, early sleep onset, and an awakening that is earlier than desired.
3. Non-24-h Sleep–Wake Syndrome (Free-Running pattern): consists of a chronic steady pattern comprised of several hours daily delays in sleep onset and wake times in an individual living in society (Fig. 2).
4. Irregular Sleep–Wake Pattern (disorganized): consists of temporally disorganized and variable episodes of sleep and waking behaviour (Fig. 3).
5. Shift work and 6. jet lag that are beyond the scope of this review.

Figures 1–3 display the rest-activity patterns of three patients suffering from Delayed Sleep Phase Syndrome, Non-24-h Sleep–Wake Syndrome and Irregular Sleep–Wake Pattern, respectively. The black areas represent activity, while the white ones represent sleep.

CRSD CHARACTERISTICS

The pioneer report by Weizman *et al.* [5], published in 1981, was followed by only a few studies, based on small numbers of patients with no more than 30 participants [6]. The only large study on CRSD patients [7] includes a survey of the characteristics of 322 patients suffering from CRSD and a case-control study comparing a group of 50 CRSD patients and 56 age and sex matched normal subjects. The major findings were: a great majority (84.6%) of the patients were found to have DSPS, 12.3% had a Non-24-h Sleep Wake Syndrome, while only a handful of patients were diagnosed with an Irregular Sleep–Wake Pattern (1.9%) and ASPS (1.3%). In a report from a sleep clinic in Japan similar data was recorded [8]. The low prevalence of ASPS in CRSD may be due to fact that ASPS is a condition that is better tolerated than DSPS. It is much easier

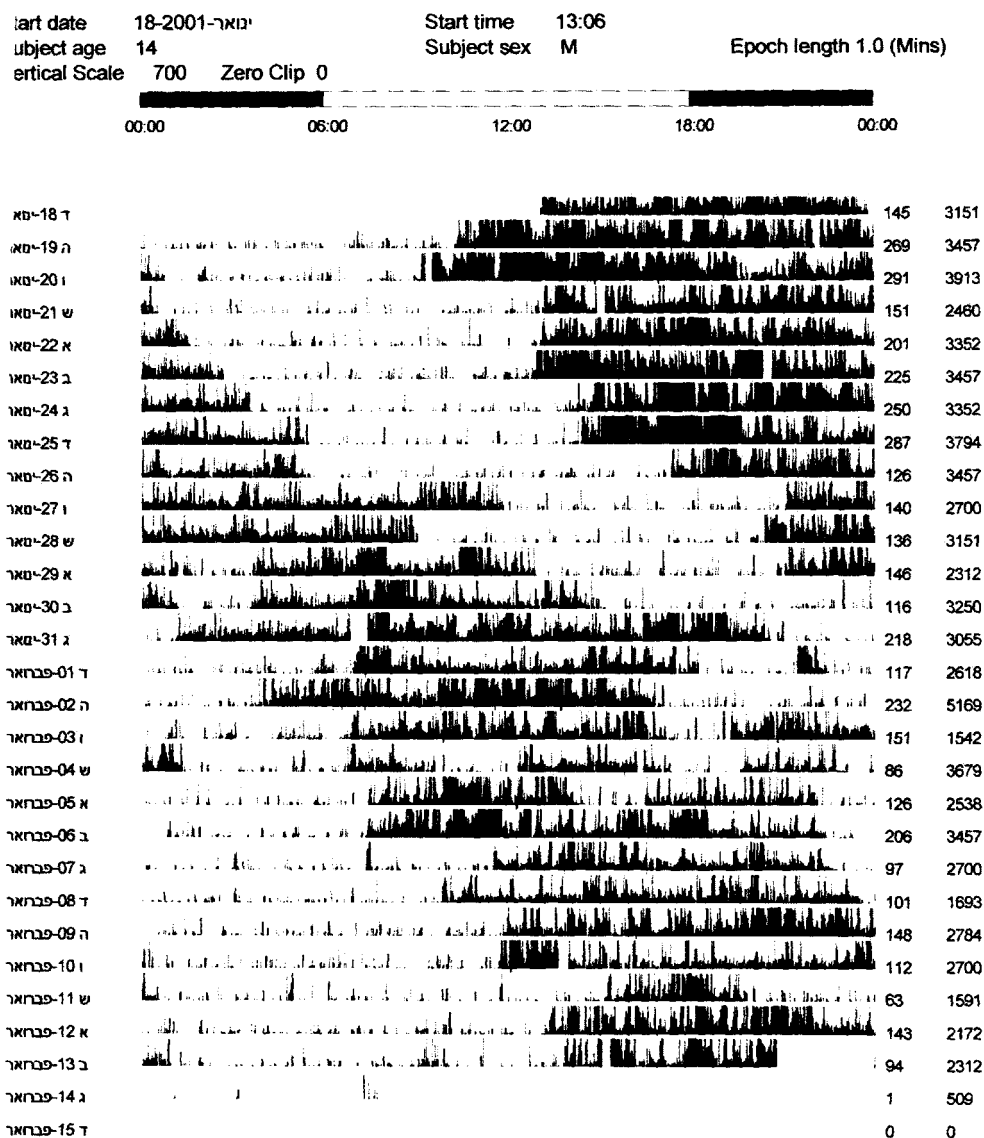


Figure 2 Non-24-Hour Sleep Wake syndrome.

to keep oneself awake for a few hours after the habitual bed-time, than to force oneself to fall asleep a few hours before one's habitual bed-time – a very frustrating if not an impossible task.

The majority of patients (89.6%) reported onset of CRSD in early childhood or adolescence; no sex differences were evident; a familial trait existed in 44% of patients.

The reported prevalence of CRSD in these studies [7, 8] reflects the population of patients who approach sleep specialists for help. There is, at the present time, very limited data available regarding the prevalence of CRSD in the general population. The prevalence of the disorder was estimated to

be 0.13% in Japan [9] 0.17% in Norway [10] and 7.3% of adolescents in the western population [11].

BIOLOGICAL ASPECTS OF CRSD

CRSD patients differ from night or morning type people ("owls" and "larks") in the rigidity of their maladjusted biological clock. While "owls" and "larks" prefer morning or evening, they are flexible and can adjust to the demands of the environmental clock. CRSD patients, on the other hand, appear to be unable to change their clock by means of motivation or education.

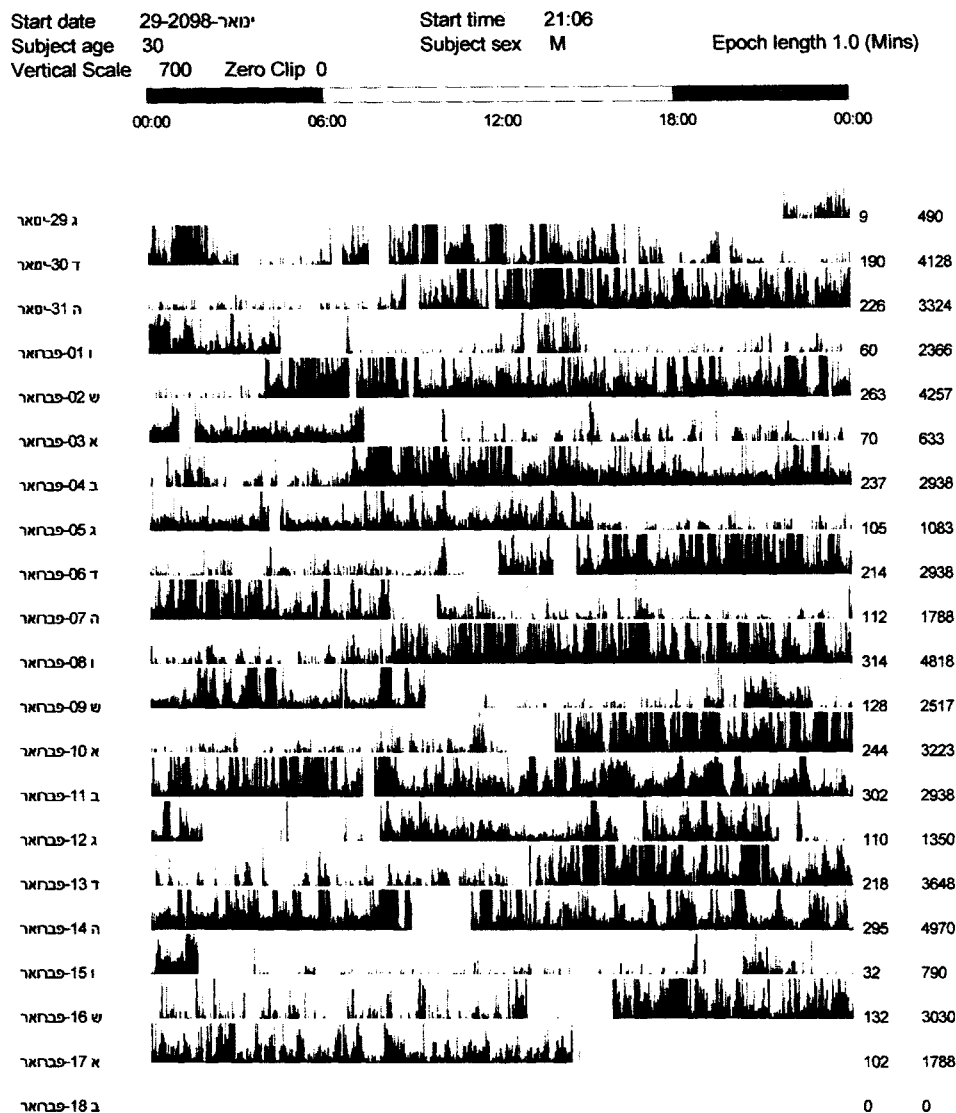


Figure 3 Irregular (or Diosorganized) Sleep Wake Pattern.

In CRSD not only the sleep–wake cycles deviates but also other circadian physiological rhythms such as: melatonin and body temperature [12–14]. The involvement of several biological rhythms in this disorder may be a part of the explanation why is it so difficult for these patients to change their sleep–wake schedule. Uchiyama *et al.* [15] looked for the cause for the inability of CRSD patients to reset sleep phase. They studied 11 DSPS patients and 15 normal control in an ultra short sleep–wake schedule measuring melatonin secretion in dim light condition. DSPS patients failed to compensate for previous sleep loss compared to control subjects. Phase angle between sleep propensity rhythms and melatonin was wider in DSPS than in controls. The

authors explain the patho-physiology of DSPS and the rigidity of their internal clock by these findings.

Another study [14] compared the core body temperature schedule of DSPS compared to normal controls. They found that sleep length and temperature nadir to sleep offset interval were significantly longer in DSPS than in the control group. They suggest, that the rigidity of DSPS patients' sleep–wake schedule is a result of their inability to phase advance their temperature circadian clock, in the same way that daily body temperature was identified as a physiological component in adjustment to shift work and jetlag [16].

Is the hereditary trend reported clinically reflected in genetic studies also? A study investigated

the human leukocyte antigen (HLA) types A, B, and DR, of 42 DSPS patients and compared its frequency with those of 117 healthy control subjects [17]. Only HLA DR1 was significantly higher in DSPS, which indicates possible association between this antigen and DSPS and maybe the genetic factor for predisposition to DSPS. Others [18, 19] suggest that several mutations in the human melatonin 1a [hMella] receptor gene are the cause of the biological rhythm disorders.

DIAGNOSIS

The best method to make the diagnosis of CRSD is by a clinical interview and a week of actigraphic monitoring or sleep log in free conditions. Monitoring the sleep–wake schedule under forced conditions can mask the pattern of the schedule thus misleading the diagnosis. The actigraph is a watch size device worn on the wrist sampling hand motion. A computerized algorithm can provide highly reliable data on sleep and wake periods of the patient [20, 21]. We believe that actigraphy is the best objective diagnostic tool for CRSD, as opposed to polysomnography (PSG), which is not an adequate tool for the assessment of CRSD. This is due to the nature of CRSD, which requires monitoring for several days in order for the patients' sleep–wake pattern to manifest itself clearly. This is very difficult to do with PSG, yet can be perfectly demonstrated by actigraphy (see Figs 1–3). Melatonin secretion and/or temperature measure for at least 36 hours every two hours can be an additional diagnostic tool, yet usually not necessary.

TREATMENT

Patients suffering from DSPS are treated with one of, or a combination of several methods, such as chronotherapy [22], light therapy [23], vitamin B12 [24], or melatonin administration [25, 26].

The term chronotherapy in sleep medicine refers to a behavioral technique in which bedtime is systematically delayed, so following the natural tendency of human biology. This is done, until sleep onset time coincides with the desired sleep time, where the conventional 24-h day is re-established. Consequently, the patient is advised to maintain the newly achieved bedtime rigidly, and from then on not to delay bedtime [27].

Administration of B12 has been reported to normalize human sleep–wake rhythm disorders such as Non-24-h Sleep–Wake Syndrome, DSPS, or insomnia. However, the mechanisms of the action of B12 on the rhythm disorders are unknown [28]. It may act by changing the ocular receptors' affinity to light, or exert a direct influence on melatonin [29], yet there is little experience with this treatment and very few accounts appear in the literature. All the reports of vitamin B12 efficiency for CRSD were based on open studies, thus the effect of vitamin B12 has not been accurately evaluated. There is only one double-blind study [30] evaluating the effect of 3 mg/day methylcobalamin or placebo administered for 4 weeks to DSPS patients. No significant differences were observed between the two groups in sleep–wake cycles and in the feeling of tiredness during the day.

Light therapy, which became increasingly popular as the importance of light in resetting the circadian system was recognized, involves using morning bright light exposure to induce a phase advance in both sleep onset and wake times [31]. Even very short term (5 days) of phototherapy on six patients with DSPS proved advancement of sleep phase and body minimum temperature [32]. Practice parameters for the use of light therapy in the treatment of sleep disorders was published by the Standards of Practice Committee, American Academy of Sleep Medicine [33]. They maintain that, light therapy has been found to be a useful treatment for DSPS and ASPS, but its benefits for the treatment of non-24-h sleep–wake syndrome, jet lag and shift work are less clear. However this treatment demands 30–60 min of sitting in front of a light-box every morning or evening, which is complicated to manage for many DSPS patients.

While chronotherapy and light therapy are demanding and difficult treatments, which usually lead to compliance problems (thus giving rise to few reports in the literature), melatonin administration, is a relatively simple and easy treatment option. Studies have shown that melatonin has a sleep-promoting and entraining action when taken in the evening. The effects of the administration of small doses of melatonin (0.5–5.0 mg.) have been shown to follow a phase-response curve that is nearly the opposite of light curve [34]. Phase advances are produced by melatonin administered in the evening, while phase delays appear when it is administered in the early morning [35]. It is also been shown

that melatonin induces temperature suppression [36], and that there is a direct relationship between the ability of melatonin to phase shift the endogenous circadian clock and its temperature suppressing quality [37]. These characteristics seem to be what makes melatonin an effective means of dealing with chronobiological disorders. In studies, where only part of them were randomized placebo-controlled, melatonin proved to be effective in: shift work induced sleep disorders [38], sleep disturbances caused by a de-synchronization of the endogenous sleep-wake cycle from lighting cues in blind, geriatric and brain damaged subjects [39] CRSD, including DSPS [25, 26, 40]. In a double-blind placebo-controlled cross-over study [41] the effect of 5 mg melatonin administration to 25 DSPS patients was investigated. The influence of melatonin was assessed by: 24-h melatonin and rectal temperature curve, polysomnography, actigraphy, sleep log and subjective sleep quality assessment. After treatment there was a significant advancement in melatonin curve (approximately 1.5 h), actigraphic and PSG sleep onset and offset and people felt more refreshed in the morning. The temperature curve did not move significantly. Another study comparing melatonin and placebo treatment for DSPS confirmed these results [42]. Recently several studies reported on the effects of melatonin on the quality of life of DSPS patients [43], for DSPS patients suffering from chronic headache [44] and for the regulation of CRSD of mentally retarded children [45, 46]. There are controversies about its usefulness in jet-lag [47, 48].

It has been shown that melatonin has an extremely wide margin of safety, at least in terms of short-term side effects. In a study that examined the effects of oral melatonin on skin color and the release of pituitary hormones, five patients with hyper-pigmented skin were given 1 g/day of melatonin orally for a period of 30 days, with minimal adverse effects. These patients did complain of increased drowsiness, but a thorough examination did not reveal any evidence of toxicity [49] despite the very high dosage used in this study (200–2000 times greater than that generally used for the treatment of circadian disorders). It should be noted that even a 0.5–5.0 mg dosage of melatonin is higher than normal nocturnal levels of melatonin in the blood. Moreover, Arendt points out that no data exist on long-term studies in humans [50], therefore questions of safety have yet to be fully researched and resolved.

Dahlitz *et al.* [25] illustrated that an oral dose of 5 mg of melatonin taken in the evening causes a significant phase advance toward conventional times of both sleep onset and awakening with no significant changes in sleep duration or architecture. Oldani *et al.* [51], treated six DSPS patients with 5 mg of melatonin for a period of one month, with similarly positive results, and no changes to sleep architecture or duration. In both studies, however, the pretreatment sleep pattern returned 2–3 days after the end of treatment [52].

While the above studies all support the efficiency of melatonin treatment for DSPS, they were all carried out on a relatively small number of DSPS patients. Over the past six years, over 400 people suffering from DSPS have been referred to our sleep and chronobiology clinic. Most of these patients were treated with melatonin based on the principles suggested by Dahlitz *et al.* [25], and received guidelines regarding maintenance of their new sleep patterns. After a substantial period of time had elapsed, we decided to conduct a subjective follow-up study [26]. In this study, we attempted to investigate the effectiveness of the treatment and the existence of any possible side effects. We also hoped to ascertain whether a relationship exists between the length of effectiveness of the treatment and certain aspects of the illness. This study, which accompanied routine treatment in our sleep clinic, examined the efficiency of melatonin treatment in a relatively large sample of DSPS subjects by means of subjective reports. A sample of 61 subjects, 37 males, and 24 females were diagnosed with DSPS by means of clinical assessment and actigraphy. Their mean pre-treatment falling asleep and waking times were 03.09 (SD = 86.22 min) and 11.31 (SD = 98.58 min), respectively. They were treated with a six-week course of treatment comprising 5 mg of oral melatonin taken daily at 22.00 h. Twelve to eighteen months after the end of the treatment, a survey questionnaire was sent to the home of each subject to investigate the efficiency of the melatonin treatment and its possible side effects. 96.7% of the patients reported that the melatonin treatment was helpful, with almost no side effects. Of these, 91.5% reported a relapse to their pre-treatment sleeping patterns within one year of the end of treatment. Only 28.8% reported that the relapse occurred within one week. The pre-treatment falling asleep and waking times of patients in whom the changes were retained for a relatively long period of time

were significantly earlier than those of patients whose relapse was immediate ($t=2.18, P<0.05$; $t=2.39, P<0.05$, respectively), with no difference in sleep duration. There are CRSD patients for whom all these treatment modalities fail to help. In these cases it becomes a CRSD Disability [53] and the only successful treatment is rehabilitation i.e. for the patient to adopt a new career that enables to work within the limits of his chronobiological disorder.

CRSD IN PSYCHIATRY

It has been found that there is a high prevalence of learning disorders (19.3%) and personality disorders (22.4%) in people who have CRSD [7]. The high prevalence of personality disorders in CRSD patients has been confirmed in a controlled study, which found that individuals suffering from CRSD are characterized to a greater extent by personality disorders than a control group [54]. In a complementary study [55] 63 hospitalized adolescents were studied. None of them had any diagnosed medical disorders, and all were being treated with psychiatric drugs. Ten subjects were diagnosed as suffering from DSPS according to a sleep-wake schedule structured interview. Subjects diagnosed as suffering from personality disorders had a significantly higher probability of also suffering from DSPS. Additional findings were that patients with DSPS were more likely to have received an DSM IV axis II diagnosis only, and were more likely to be diagnosed as suffering from a distinct group of disorders characterized by affective lability. The findings of DSPS and personality disorders, may lend some support to the hypothesis that inborn peculiarities in the sleep-wake rhythm lead to the social and functional difficulties characteristic of personality disorders.

Learning disorders and even personality disorders are related or may even be an outcome of CRSD. A child who does not get enough sleep at night will not be alert during the day in school, and is prone to have trouble keeping up with the other children. Frequently, the patients' parents, teachers, doctors, or psychologists believe that the patients' biological sleep-wake problem and the accompanying dysfunction at school are motivational or psychological in nature, a belief that during the years, the patients tend to adapt themselves. This attitude toward

CRSD patients, to which he or she has been subjected since early childhood or adolescence, adds psychological distress to the practical difficulties of coping with life. Several studies found depression to be frequent in DSPS [6, 56, 57] Is it an outcome of their failure to adjust to the environmental everyday life demands or simply symptoms of fatigue as a result of ongoing partial sleep deprivation?

Attention Deficit Hyperactive Disorder (ADHD) has also been found to be related to the instability of the sleep-wake system [58]. Thirty-eight school-age boys with ADHD and 64 controls were examined with actigraphs and sleep diaries over five consecutive nights. Discriminant analysis revealed that children's classification (ADHD versus control) could be significantly predicted on the basis of their sleep-wake patterns.

Sleep disorders are a common symptom and characteristic of numerous psychopathologies such as depression, anxiety, PTSD etc. We wish to emphasize the fact that no existing psychopathology is characterized by a sleep disorder of the circadian type.

DRUG-INDUCED CRSD

Can pharmacological treatments cause CRSD as a side effect? Wirz-Justice *et al.* [59], describe a case of a patient with chronic schizophrenia, treated with haloperidol, and showing signs of CRSD. Changing medication to clozapine showed a direct effect on his sleep and established a more organized sleep-wake pattern. Another report [60] is of a 22 year-old male patient who was diagnosed at the age of 16 as suffering from Tourette Syndrome and severe OCD. The Tourette Syndrome has been successfully treated with haloperidol for 6 years. After 2 years of treatment with haloperidol he began showing signs of disorganized sleep, which clearly were not present before. The patient complained of difficulties in falling asleep at a regular time and a severe problem in awakening at the desired time for daily activity. The problem has caused him severe difficulties in day-to-day functioning and due to this he was unable to keep a job on a regular basis. He was a very talented computer systems analyst and had started to work from home during the hours he was awake.

A night of polysomnography revealed no sleep apnea. Three weeks of actigraphy done in a free running condition showed a disorganized sleep-

wake schedule. The patient was taken off the haloperidol and was given risperidone 1 mg/day. He reported an improvement in his sleep difficulties and no worsening of his Tourette symptoms. A revised actigraphic monitoring confirmed the patient's subjective feeling. Additional 5 mg oral melatonin taken at 21.00 h was added to the risperidone and a full recovery was documented in a third follow-up actigraphy. This was accompanied by his feeling of a significant improvement. The patient was unable to find enough superlatives to describe the change in his life. After years of difficulties in coping with his occupational and social life due to unconventional sleep timing, he at last started to have an organized schedule that has enabled him to recover his diurnal life.

Is haloperidol the only psychiatric drug that can provoke CRSD? Hermesh *et al.* [61] reported on ten patients who developed typical DSPS during treatment with the specific SRI agent fluvoxamine (FVA), prescribed for their obsessive-compulsive disorder. The delay in falling asleep ranged between 2.5–4 h later than the patients' normal sleep routine. In the first five patients, DSPS was initially misdiagnosed as FVA induced somnolence or sedation. The causal role of FVA in the development of DSPS in this series is corroborated by several pieces of clinical evidence: FVA was the only drug taken by these patients. In all patients, first appearance of DSPS had occurred following FVA initiation. In all 10 cases, where FVA was withdrawn, or the dose considerably decreased, DSPS disappeared. Re-exposure of 3 patients to FVA again led to the return of DSPS. No case of spontaneous remission of DSPS was observed, even when FVA was administered for longer than 2 years (range 5.5 weeks–2.2 years). Emergence of FVA-induced DSPS was not immediate, and at least 5 days of ingestion, with no less than 100 mg/d of FVA, had passed before patients first notice the change in their normal sleep pattern. The authors conclude that FVA can cause DSPS, which is often overlooked by the clinician or misdiagnosed as psycho-physiological insomnia. Additional treatment with melatonin 5 mg at 21.00 h can re-organize the sleep–wake schedule of these patients thus enable to continue the FVA use.

CRSD AND HEAD TRAUMA

It has been found that certain people have developed CRSD after head trauma, even when the trauma is

minor [62]. This group is usually characterized as suffering from Disorganized Circadian Rhythm Sleep Disorder [DCRSD] with onset later than is common for other types of CRSD. This is opposed to the findings of Quinto *et al.* [63], who described one case of DSPS and not DCRSD occurring after brain trauma and the findings of Negtegaal *et al.* [64]. In all the cases there were no objective pathological finds in imaging (CT, MRI or EEG), and no cognitive dysfunction, but patients complained of difficulty in falling asleep and waking up as well as sleepiness during the day. All of the patients had no complaints of sleep–wake cycle inconsistency previous to the trauma, but all of them had been misdiagnosed for years following their injury. The diagnoses were often psychiatric in nature, and often mistreated pharmacologically. Some cases were given the psychological diagnosis of PTSD (Post-Traumatic Stress Disorder) although they did not meet the criteria for PTSD. Many patients were just thought to be malingering in order to gain financially from their accident.

While treatment with melatonin is useful in DSPS, it has been found to be little or no help in treating DCRSD following head trauma [62]. Since there is no effective pharmacological therapy, the approach to CRSD after head trauma should be rehabilitation [53]. As with any other disability following physical trauma, the patient must understand and accept that the disability is permanent and should be guided in overcoming it. The patient should be encouraged to consider changes in his daily lifestyle, possibly a change of occupation that conforms more to the hours he is awake, possibly, in certain cases, working from home, and setting his own timetable.

It is not yet clear why minor head trauma causes the onset of CRSD. Possibly there is a micro damage to the pathways that are responsible for the synchronization between internal and external clocks. It is also possible that this damage is the reason why we are unable to treat DCRSD brought on by head trauma successfully with melatonin.

CONCLUSION

CRSD are sleep pathologies rarely familiar to doctors. Many of our CRSD patients had, for years, been wrongly diagnosed by neurologists, pediatricians and especially by psychiatrists as psycho-physiological insomniacs, and therefore unsuccessfully treated, usually with sleeping pills [7]. Early onset of CRSD,

the ease of diagnosis, the high frequency of misdiagnosis and erroneous treatment, the potentially harmful psychological and adjustment consequences, and the availability of promising treatments, all indicate the importance of greater awareness of these disorders. Doctors from various specialties: pediatricians, family doctors, psychiatrists, neurologists, as well as psychologists and teachers should be more alert to the existence of CRSD.

Practice Points

When patients complain of sleep difficulties the doctor should ask some additional clinical questions about their sleep–wake habits.

If CRSD is suspected, we suggest asking some more questions:

1. Hunger times: the patient should be questioned about his/her preferable eating hours – whether she/he eats or is hungry during the night, and whether she/he ever eats early in the morning
2. Hours of alertness: DSPS patients, even when they wake up early and should thus become more and more tired as the day passes, will paradoxically become more alert as evening approaches.
3. Heredity: patients should be asked about close family members with the same characteristics.
4. Functional difficulties: CRSD patients often have trouble functioning in everyday life. The hallmark of their problem is a severe difficulty to wake up at the morning.
5. Rigidity of the biological rhythm: CRSD patients have very rigid biological clocks. Therefore, it is extremely difficult for them to adjust to environmental demands, even for a very limited time. They should be asked about their sleep–wake habits during vacation time.
6. Head Injury: patients displaying symptoms of an Irregular Sleep–Wake Schedule should be inquired about prior head injuries (even minor).
7. Drugs side-effect: It is advised for psychiatrists treating patients with psychotropic drugs to take into consideration CRSD as a possible side effect of this group of drugs.

Research Agenda

1. The prevalence of CRSD in the general population is yet unknown and requires a study.
2. More has to be done in order to understand the biological mechanisms involved in the desynchronization of CRSD patients biological rhythms.
3. The hereditary trend of CRSD should point to studies on the genetic basis of the disorder.
4. Are there more drugs for which CRSD is one of their possible side effects?
5. More research needs to be done on the safety and efficacy of CRSD treatments, including light therapy and melatonin.

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