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CIRCADIAN RHYTHM SLEEP DISORDERS RELATED TO AN ABNORMAL ESCAPE OF THE SLEEP-WAKE CYCLE

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Delayed sleep phase syndrome

Historical Background

In 1981 Weitzman and colleagues gave the first description of a new disorder, the delayed sleep phase syndrome (DSPS), after an extensive evaluation of a subgroup of insomniac patients at the Montefiore Hospital Medical Center (Weitzman et al., 1981). They reported delayed sleep patterns in 30 out of 450 insomniac patients (7%) studied between 1976-1979. These patients were younger (33 $\pm$14 y.o.) than the general population of insomniacs (46 $\pm$15 y.o.) and were described as having extreme evening chronotypes. The sleep problems were often present for several years and frequently began during childhood. In 7 of these patients, the disturbed sleep pattern was reported to have started prior to the age of 10, though occurrence at other ages is also possible. In Weitzman's study, no sex differences were reported although most subsequent accounts have stressed a male predominance of about 10:1. Since then, over 75 cases have been described (Alvarez et al., 1992; Regestein et al., 1995; Dahlitz et al., 1991).

Epidemiology

DSPS is one of the most common circadian rhythm sleep disorders (Oldani et al., 1994; Dagan et al., 1996; Okawa et al., 1997; Coleman, 1983). It is generally estimated that 7-10% of insomniac patients might suffer from DSPS and that this number might even be underestimated (Weitzman et al., 1979; Czeisler et al., 1991). Indeed, sleep onset insomnia is one of the most frequent types of insomnia and is more prevalent among younger patients with the peak prevalence among high school and college students (Richardson et al., 1996; Morris et al., 1990; Billiard et al., 1993b; Ito et al., 1993). An epidemiological study in the San Francisco Bay area revealed that sleep-onset insomnia had an earlier age of onset (37 y.o.) as opposed to early morning awakening (40.2 y.o.). The most prevalent pattern of sleep disruption in younger patients (18-30 y.o.) was sleep-onset insomnia and the least prevalent was early morning awakening (Bixler et al., 1979). The incidence of DSPS is estimated to be $\geq$ 7% in adolescents compared to less than 0.7% in the general population (Wagner, 1996; Regestein et al., 1995). Several epidemiological studies have been conducted in populations of students using sleep questionnaires. Students with DSPS went to bed more than 2 hours later on weekends and suffered from sleep-onset insomnia and insufficient sleep on week nights (Lack, 1986). Interestingly, a sleep questionnaire administered to 277 students revealed that poor sleepers generally felt less tired in the evening than good sleepers (Kirmil-Gray et al., 1984) suggesting a chronobiological basis. The Standford Sleep Inventory, administered to 639 adolescents revealed chronic and severe sleep disturbances in 12.6% of the sample population (Price et al., 1978). Difficulty falling asleep was observed in 74.8% of those reporting chronic sleep difficulties and in 60% of those reporting occasional difficulties. A higher proportion of adolescents suffering from chronic sleep problems enjoyed staying up at night (79.5%) compared to healthy sleepers (59.9%) (Price et al., 1978).

Positive diagnosis

According to the International Classification of Sleep Disorders (ICSD, 2001), DSPS is characterized by an inability to fall asleep or to awaken spontaneously at the desired times and a phase delay in the main sleep episode. Sleep quality, sleep stage distribution, and sleep duration are normal when patients are not forced to maintain a strict schedule and instead allowed to sleep at their desired times. However, sleep latency is frequently longer than 30 minutes even if patients go to bed at times of their choosing (Wagner, 1990). When sleep is planned earlier (e.g. 23h00), a significant increase in sleep latency and wake time during the first part of the night is observed (Allen et al., 1989). These patients are entrained to a 24-hour day and go to bed at about the same clocktime every night. However, patients are extreme night owls such that sleep onset and wake times are intractably later than desired (Czeisler et al., 1991). Bedtimes are frequently observed around 3-6 h with waketimes around 10-15 h if the patients are not disturbed. In DSPS, the average sleep duration on weekdays varies from 2 to 5 hours per night with a tendency to recuperate on the week-ends by sleeping 9-18 hours per night. Excessive sleepiness is generally experienced in the morning following awakening (Rosenthal et al., 1990), such that severe difficulties awakening at socially acceptable times are reported. As a result, a significant proportion of DSPS patients report disrupted work or social functioning (Regestein et al., 1995; Alvarez et al., 1992). A diagnosis of DSPS should be confirmed by a sleep/wake log and ideally wrist actigraphy monitoring for at least one month (Rosenthal et al., 1990). Polysomnographic recording of 1 or 2 nights should be planned at the patient's preferred sleep time (Weitzman et al., 1981). The disturbances of their sleep/wake cycle should not be explained by other psychiatric or medical conditions. Some patients have delayed sleep patterns but are able to advance their bedtime earlier due to social pressure. These patients should rather be assigned a diagnosis of motivated sleep phase delay rather than DSPS (Schrader et al., 1996).

Pathophysiology

In humans, it is possible to induce sleep-onset insomnia by scheduling subjects to live on shorter than 24-hour days, presumably because bedtime would coincide with the so-called evening wake maintenance zone (Strogatz et al., 1987; Fookson et al., 1984). Strogatz suggested that DSPS could result from delayed core body temperature rhythms that would then align the wake maintenance zone with bedtime (Morris et al., 1990). Indeed, delayed rhythms of plasma melatonin, urinary 6-sulfatoxy melatonin, and core body temperature have been reported in DSPS (Oren et al., 1995; Ozaki et al., 1988; Ozaki et al., 1996) but one cannot determine if these are a consequence rather than a cause of delayed sleep times. Recent studies suggest that individual differences in the increase of the circadian period might lead to a different phase relationship between the endogenous circadian pacemaker and the sleep/wake cycle (Duffy et al., 1996b). Based on core body temperature and melatonin onset, a circadian period slightly longer than normally reported in adults was found in adolescents (Carskadon et al., 1999). Despite these results of an increased period, it is improbable that this sole difference could account for the daily difficulties in falling asleep. Another possibility is that the duration or strength of the evening wake maintenance

zone is enhanced in patients with DSPS or that patients have stronger wake mechanisms (perhaps a faulty homeostatic drive for sleep) that pushes them to delay sleep onset to a time of increased sleep propensity, namely later at night. Indeed, there is compelling evidence to suggest that DSPS patients go to bed on the rising limb of their core body temperature cycle close to the circadian temperature nadir (Ozaki et al., 1988)(Figure 1). The phase angle between the time of awakening and the temperature nadir was found to be significantly larger in DSPS patients (3.78 hours) compared to controls (2.86 hours) (Ozaki et al., 1996)(Figure 2). This indicates that DSPS patients tend to go to sleep at later circadian phases, a situation that results in a shielding of the phase advance portion of the phase response curve to light and thus a worsening of their tendency to delay sleep times. This could also explain why DSPS patients are at risk to develop a non-24-hour sleep/wake syndrome.

Differences among individuals might exist with respect to their sensitivity to light as a circadian synchronizer (Weitzman, 1981). In DSPS, it was proposed that the phase advance portion of the phase-response curve to light is weaker than normal but that some phase advance still occurs in order to stabilize the sleep/wake cycle to the 24-hour environment (Czeisler et al., 1991; Czeisler et al., 1983; Weitzman et al., 1981). Alternatively, one could also hypothesize an increased sensitivity to evening light. This could delay the start of melatonin secretion and the so-called opening of the sleep gate until later at night. In support of this hypothesis, the percentage of melatonin suppression by a bright light stimulus of 1,000 lux administered 2 hours prior to the melatonin peak has been reported to be greater in 15 DSPS patients than in 15 controls (Aoki et al., 2001).

Several case studies have been published reporting of patients who developed DSPS after traumatic brain injuries or whiplash (Quinto et al., 2000; Patten et al., 1992; Nagtegaal et al., 1997). It has been hypothesized that suprachiasmic nucleus (SCN) lesions or lesions of the cervical projections from the SCN to the pineal gland could be responsible for the deficits. However, so far, no group has been able to relate this condition to any specific lesion.

Whether patients with DSPS have a higher incidence of personality disorders that could contribute to their delayed sleep pattern remains unclear. So far, no specific profile of personality disorders has been identified (Weitzman et al., 1981; Dagan et al., 1996; Wagner, 1990; Weitzman et al., 1979). About 50% of DSPS patients have some psychopathology (Alvarez et al., 1992; Weitzman et al., 1981) and depression is the most frequent psychiatric condition associated with DSPS (Regestein et al., 1995; Okawa et al., 1997). Conversely, there is a high incidence of DSPS in depressed patients and there is a good possibility that antidepressants such as MAOI and SSRIs might contribute to the appearance of DSPS by promoting alertness and delaying sleep patterns (Regestein et al., 1995). The analyses of 63 hospitalized adolescents in a psychiatric ward revealed that 10 patients (15.9%) had DSPS (Dagan et al., 1998). It has been suggested that sleep deprivation associated with DSPS could lead to depression or that late sleeping could aggravate or precipitate depression (Regestein et al., 1995). This possibility cannot be excluded even though sleep deprivation often exerts an antidepressant effect in depressed

populations. The general interpretation is that sleep-onset insomnia is not dependent on psychological problems but psychological problems might rather be a consequence of sleep disturbances (Richardson et al., 1996). Indeed, an improvement in social and psychological functioning was reported in many DSPS patients after chronotherapy (Weitzman et al., 1981). This was at least the case of a 24 y.o. man in the navy who had been court-martialed for absenteeism due to DSPS (deBeck, 1990). The psychiatric evaluation was reported to be normal.

Treatment

Hypnotic medications are usually ineffective in entraining the sleep/wake cycle of DSPS patients and the use of drugs or alcohol may even worsen the problem of morning drowsiness (Weitzman et al., 1981). Weitzman and colleagues reported the first successful cases of chronotherapy (Weitzman et al., 1981; Czeisler et al., 1991). This was achieved by scheduling the patients to live on several consecutive 27-hour days until the desired bedtime was achieved (Figure 3). This particular duration was chosen in order to exceed the natural tendency of the endogenous circadian system to delay while staying at the upper limit of its range of entrainment. This resulted in a disappearance of sleep disturbances and the withdrawal of the hypnotic medication for several consecutive weeks and months. The bedtime and waketime advanced 1-4 hours earlier (Czeisler et al., 1991) and alertness levels significantly improved in the morning. The patients fell asleep faster and slept better on the new socially acceptable schedule. In comparison, acute phase advances of the sleep schedule results in increased sleep disturbances on the second night despite substantial sleep deprivation (Czeisler et al., 1991). Chronotherapy using 27-hour days was able to successfully advance the core body temperature rhythm from 4h00 to 22h00 in 4 DSPS patients (Ozaki et al., 1988). Prior to the intervention, the sleep onset occurred 2.7 hours prior to the temperature minimum. Following the intervention, it occurred at a more conventional phase, namely 5.3 hours before the temperature minimum. However, the delayed sleep pattern tended to relapse and several patients have found it necessary to repeat chronotherapy at 6- to 12-month intervals. After the report of DSPS patients who developed a non-24-hour sleep-wake syndrome with delayed chronotherapy, it was argued that small advances of the sleep schedule with bright light exposure would be safer (Oren et al., 2001). However, circadian rhythms disorders are typically difficult to treat, and others believe it is easier to utilize the natural tendency of endogenous circadian rhythms to delay than to fight against its current. Variants of the initial chronotherapy have been reported and comprise a combination of sleep deprivation and smaller advances (e.g. 15-minutes) of the sleep/wake cycle. These approaches were rarely efficient by themselves and were combined with other circadian synchronizers such as morning exposure to bright light, sunlight or evening administration of exogenous melatonin (Wagner, 1996; Alvarez et al., 1992; Regestein et al., 1995). For example, a 29 y.o. woman with DSPS from the age of 16 with delayed sleep onset until 4:00 had made unsuccessful attempts to advance her sleep times. She was treated using a combination of light restriction in the evening for 2 hours and a 2-hour exposure to 2,500 lux upon awakening. Her bedtimes were slowly and progressively advanced by 15 minutes each day and naps were forbidden. After 3 weeks of treatment, she was sleeping from 23h to 7h and exposing herself to 1 hour of bright light daily

(Weyerbrock et al., 1996). However, it seems difficult to keep the therapeutic effect of chronotherapy for a long time, even when other therapeutic approaches are added (Ito et al., 1993). Overall, the failure rate for treatment of DSPS (52%) is greater than that for narcolepsy (10%) or for mixed insomnia (36%) (Regestein et al., 1995).

In 1990, Rosenthal and colleagues (1990) investigated the therapeutic effects of bright light in a crossover study of 20 DSPS patients. The active condition consisted of a 2-hour exposure to 2,500 lux full spectrum light from 6:00-9:00 and the use of dark goggles in the evening from 16:00 until dusk (Rosenthal et al., 1990). After dusk, the lighting was restricted to 1 or 2 bedside lamps. In the control condition, patients were exposing themselves to 300 lux full spectrum bright light from 6:00-9:00 and used clear goggles in the evening. The patients rated the treatment condition as superior. Morning alertness levels improved during the 2nd week of the 2-week treatment and earlier sleep times were noticed under the active condition. A significant phase advance of the diurnal rhythm of core body temperature was observed in the treatment condition. Other cases of successful treatment with morning bright light or sunlight exposure have subsequently been reported (Regestein et al., 1995; Dagan et al., 1991; Joseph-Vanderpool et al., 1989).

An animal model of DSPS can be produced by keeping rats in constant darkness for several months and returning them to a light/dark cycle of 12h/12h (Armstrong et al., 1993). Among these rats, the onset of activity often lags behind the onset of darkness by 3-4 hours. Exogenous administration of a melatonin agonist, S20098, just prior to darkness can eliminate this negative phase angle. Successful treatment of DSPS was also reported in humans using 5 mg of exogenous melatonin in the evening for several consecutive weeks (Dahlitz et al., 1991; Dagan et al., 1998; Oldani et al., 1994; Nagtegaal et al., 1997). The medication significantly advanced sleep onset by 82 minutes and waketime by 117 minutes (Dahlitz et al., 1991). Several studies indicate that the timing of melatonin administration is crucial and should be planned several hours prior to bedtime for maximal efficiency (Sack et al., 1997). However across studies no consistent changes in sleep structure were reported and both melatonin and S20098 failed to permanently change the phase angle between circadian markers and the sleep schedule. These results suggest that melatonin may exert a direct hypnotic effect on the sleep/wake cycle rather than phase shifting the endogenous circadian system to an earlier time. Similar results have been reported with triazolam, a short acting benzodiazepine, which has been shown to successfully advance the sleep schedule of DSPS patients (Joseph-Vanderpool et al., 1988).

In the last 10 years, several patients with DSPS successfully treated with vitamin B12 have been published (Okawa et al., 1990; Ohta et al., 1991). It has been hypothesized that B12 administration could phase advance and improve the human circadian system's sensitivity to light (Honma et al., 1992). However, animal studies do not clearly support this hypothesis (Ebihara et al., 1996) and a recent multicenter double blind study with 55 DSPS patients suggest that prior reported success might be largely explained by a placebo effect (Okawa et al., 1997). Unfortunately, the sleep/wake schedule was not properly controlled in this last study and partial improvement has been reported in another double blind study (Takahashi et al., 1999). Further experiments are thus needed to clarify this issue.

Advanced sleep phase syndrome

Historical Background and epidemiology

Advanced sleep phase syndrome (ASPS) was originally reported in older individuals and is extremely rare in younger patients unless depression is present. In 1986, Moldofsky and colleagues reported the case of a 62 y.o. man who had been suffering from early sleep-onset and early morning awakenings for 8 years. The patient had also been treated for hypothyroidism and depression 4 years before. No depressive symptoms were noted on the SCL-90 questionnaire although an in-depth psychological evaluation was not performed and the initial polysomnographic recording revealed an abbreviated REM latency. The patient also exhibited a sleep apnea index of 17/hour and his mean sleep latency was pathological during the multiple sleep latency test (MSLT) with one sleep onset REM period. Chronotherapy was used as an attempt to delay his bedtimes. He was scheduled to live on 21-hour days for 2 weeks and stabilized for one week on a 23h00 to 7h00 sleep schedule. He was able to maintain this schedule for 5 months without early morning awakenings or daytime somnolence. However, sleep stage transition did not improve after chronotherapy. This case has thus confounding diagnoses. At the same time, Czeisler and colleagues reported the case of a 66 y.o. woman with early sleep times and an early endogenous temperature minimum (Czeisler et al., 1986). They were able to phase delay the endogenous component of her core body temperature cycle without changing her sleep schedule.

Later on, Singer and Lewy, described the case of a 38 y.o. woman who struggled with evening sleepiness and early morning awakening (Singer et al., 1989). If the patient went to bed past 00h00, she would still be awake at 4h-5h00. They treated her with bright light exposure of 2,500 lux from 20h00 to 22h00 for 2 weeks then from 21h00 to 23h00 for 2 additional weeks. The timing of her main sleep episode was free but naps were forbidden. Her sleep episodes delayed from 22h52-3h28 to 23h11-5h01 and her dim light melatonin onset delayed by 50 minutes from 19h50 to 20h40. In 1993, Billiard and colleagues published the first case of a 15 y.o. caucasian girl with early evening sleepiness, early bedtime (18h00-20h00) and early morning awakening (4h00-6h00) (Billiard et al., 1993a). The disturbed sleep schedule was present since childhood and similar symptoms were reported in her mother and maternal grandfather. The diagnosis was confirmed by 3 weeks of actigraphy recording. A polysomnographic recording revealed a sleep onset at 20h09, an abbreviated REM latency of 6 minutes, and an early morning awakening at 1h39 resulting in reduced total sleep time of 4h49 minutes. Some recuperation was noted on the second night. She was successfully treated using chronotherapy with a 3-hour advance of her bedtime each day. The success was short lived as she relapsed after 2 weeks.

Positive diagnosis

ASPS is often described as been the old-age equivalent of DSPS but with sleep times that are intractably earlier than desired. ASPS is characterized by evening sleepiness, sleep onset

around 18h00-21h00 and early morning awakening around 1h00-3h00 (Wagner, 1996). Sleep recording performed at the patient's desired sleep time is normal. However, when the patient attempts to sleep at later times, evening sleepiness, early morning awakening and reduced total sleep time are reported. The diagnosis should be confirmed by wrist actigraphy for several weeks at home and a laboratory investigation comprised of 2 polysomnographic recordings at the patients' best time. A MSLT could also be useful to confirm the diagnosis (ICSD, 2001). Intrinsic sleep disorders such as sleep apnea/hypopnea should be ruled out and no pathological sleepiness should be present during the MSLT. Sleep structure and efficiency should be normal if the patient sleeps at their desired time. A major depressive illness should be suspected if reduced REM sleep latency is present (Wagner, 1990).

Pathophysiology

Complaints about disturbed sleep and insomnia appear more frequently in the elderly than in any other age group and its prevalence is estimated to be between 15 and 50% (Dement et al., 1982; Lorrain et al., 1997; Buysse et al., 1991). Older subjects tend to go to bed at an earlier time, get up early, and sleep less at night than younger subjects (Czeisler et al., 1992; Reyner et al., 1995; Campbell et al., 1993). These changes appear progressively in life as they start to be observable in middle-aged individuals (Monk et al., 1995; Carrier et al., 1999). We might hypothesize that ASPS is an exaggeration of the normal tendency to advance sleep time with aging or we might hypothesize that ASPS patients are extreme and pathological cases of morning larks. However, more studies are needed to clarify the phase angle between circadian markers and the sleep/wake cycle in patients with ASPS. Changes in circadian propensity with age cannot be summarized by simply considering the elderly as morning-type subjects. We know from the studies by Duffy and colleagues (Duffy et al., 1999a) that the differences observed between old and young subjects in the phase relationship between awakening and the temperature nadir is different from that observed between young morning-type and evening-type subjects. The authors reported that older subjects tend to wake up earlier than younger subjects but that they would also wake up at an earlier circadian phase than young morning-type subjects would. They would thus expose themselves to light earlier in the circadian cycle at a phase when it would further reinforce advances of the circadian system. This phase relationship is more comparable to that of young evening-type subjects who would also wake up early in their circadian cycle, enhancing any phase advancing effects of light exposure. This phase relationship in young evening-type subjects could possibly compensate for a weaker tendency to phase advance with light exposure. In young morning-type subjects, the temperature minimum is observed earlier within the sleep episode, which implies that a larger delay portion of the phase-response curve (PRC) is exposed to evening light. This phase relationship in young morning-type subjects could possibly compensate for weaker phase delaying mechanisms. It has been suggested that a reduced circadian period and/or partial defect in phase delaying mechanisms could be involved in the physiopathology of ASPS (Wagner, 1996). Interestingly, a significant correlation between circadian period and the chronotype was observed, with young morning- and evening-type subjects having the shortest and longest periods, respectively (Duffy et al., 1999b). A familial form of ASPS has also recently been

associated with a defect in the phosphorylation of the human homologue of the *period* gene in Drosophila (hPer2) (Toh et al., 2001). However, not all patients are equally affected and familial ASPS is thought to be a heterogeneous condition.

Treatment

Historically, chronotherapy in patients with ASPS has been designed to work in the opposite direction than for patients with DSPS and to exploit the presumed greater phase advancing capacity of these patients. Typically, patients are scheduled to live on 21-hour days until they go backwards around the clock and reestablish socially acceptable bedtimes and waketimes. Small, progressive delay shifts in bedtimes by ~15 minutes/day may also be attempted (Baker et al., 2001). As for DSPS, patients should rigorously comply with the new schedule as the risk of relapse seems high (Billiard et al., 1993a). Any deviation from the establish routine (e.g. by going to bed too early one night) would then shield the delay portion of the phase response curve to light and reinforce the natural tendency of the patient to advance the timing of his sleep episodes. This would lead to early morning awakenings and light exposure on the most sensitive part of the advance portion of the phase response curve to light. Since the light/dark cycle is the most powerful synchronizer of human circadian rhythms (Czeisler et al., 1989; Boivin et al., 1996), therapeutic manipulations of the sleep/wake cycle should be reinforced by judicious exposure to light and darkness. Bright light in the evening will promote delay shifts and be an effective treatment of ASPS. Indeed, Campbell and colleagues (1993) have successfully treated 16 ASPS patients with this approach. A 2-hour session of exposure to 4,000 lux prior to bedtime for 10 days produced a significant phase delay shift of their core body temperature rhythm (-3.13 hours). The bright light exposure tended to delay the onset of sleep and waketime by 29 and 18 minute, respectively. The temperature minimum regained a more appropriate position within the sleep episode after the bright light treatment (Figure 4). As a result, patients treated with bright light saw their sleep efficiency increased from 77.5% to 90.1%, with fewer awakenings especially in the second third of the night. REM latency also increased. Similar results have been reported in 5 women and 10 men aged 32-77 years complaining of early morning awakening (Lack et al., 1993). Core body temperature and urinary 6-sulfatoxymelatonin was assessed prior and after a bright light treatment using 26-hour constant routine procedures. In the treatment condition, patients were exposed to 2,500 lux from 20h00-24h00. They remained in ordinary room light of 150 lux in the control condition. Bright light exposure phase delayed the core body temperature rhythm by 2-4 hours and the urinary 6-sulfatoxymelatonin rhythm by 1-2 hours. Sleep onset remained unchanged but patients woke up 1 hour later.

Exogenous melatonin administered in the morning was also proposed based on the PRC to melatonin (Lewy et al., 1992). However, there is a lack of strong data supporting phase delaying properties of S20098 or melatonin such that their potential use in ASPS is uncertain (Armstrong et al., 1993).

Non-24 hour sleep-wake (or hypernychthemeral) syndrome

Historical Background

In 1970, Eliott and colleagues (1970) described the first case of a man living on 26-hour days. Unfortunately, the authors did not clarify whether the patient was blind, suffered from a psychiatric disorder, or made voluntary attempts to entrain to the 24-hour day. So far, most cases have been described in either blind patients (Miles et al., 1977a; Okawa et al., 1987; Folkard et al., 1990; Nakagawa et al., 1992; Lapierre et al., 1995) or in patients with schizoid and introvert personality disorders (Eastman et al., 1988; Ferber et al., 1983; Giedke et al., 1983). For instance, Miles and colleagues (1997a) described the case of a psychologically healthy 28 y.o. blind man, actively working, with severe and cyclic sleep-wake disturbances (Figure 5). Circadian rhythms of core body temperature, alertness, performance, cortisol, and urinary electrolytes excretion were free running with a period longer than 24 hours. The patient was suffering from insomnia and excessive daytime sleepiness every 20 weeks or so. When he slept at his desired times, he spontaneously adopted a sleep-wake cycle of 24.9 hours and was asymptomatic. Attempts to entrain his sleep-wake cycle with hypnotics and stimulants were unsuccessful. A 10-day trial on a 24-hour schedule was attempted when his core body temperature arrived in phase with his sleep-wake cycle. Sleep recordings were normal during the free-running section but sleep significantly deteriorated during the attempts to synchronize to the 24-hour day. In this case, sleep onset and wake after sleep onset increased whereas total sleep time, stage 4 sleep, and REM sleep decreased. Growth hormone secretion remained associated with the occurrence of sleep whereas cortisol remained more tightly coupled with the endogenous circadian system and free-ran regardless of the imposed sleep-wake cycle.

Other cases of non-24-hour sleep-wake syndrome have been described. For instance, Kokkoris and colleagues (1978) described the case of a 34 y.o. man who maintained a sleep-wake cycle of about 24h20 for an 8-year period. Core body temperature was recorded over 3.5 months and the patient filled out a sleep-wake log for 6 months. He reported better sleep and alertness when his sleep episodes coincided with the low points of his core body temperature rhythm. The patient also had a schizoid personality that might have contributed to his lack of entrainment to the 24-hour day. In 1980, Weber and colleagues (1980) described the case study of two sighted college students who maintained a longer-than-24-hour sleep-wake cycle for nearly 4 years. John, a psychology student kept a sleep-wake diary from the age of 24 to 28 years in order to analyze the environmental determinants of his own behavior. Mary, apparently his friend, was a research assistant in psychology with a flexible work schedule. She kept a diary for 1 year primarily due to John's influence. There is no clear indication that these subjects suffered from their unusual schedule, which seemed to depend on a voluntary decision. The subjects were sleeping on average 7.6 hours per day. When faced with social demands, John attempted to adjust to a 24-hour rhythm by keeping regular waketimes but he needed several alarm clocks to wake up in the morning for his classes. The analysis of his sleep-wake log revealed some sections, especially during the summer vacation period, during which he maintained a regular 24-hour schedule, although at a delayed time. His disturbance is thus more compatible with a DSPS

than with an hypernychthemeral syndrome. Similar observations can be made of Mary. In 1986, Wollman and Lavie reported the case of a 26 y.o. man who for over 4 years had an inability to wake up and a greater than 24-hour sleep-wake cycle. The patient was described as extremely introvert with neurotic, narcissistic and borderline personality traits. The neurological exam was normal. A sleep diary kept for 4 years revealed an average day length of 27.4 hours. However, the analyses included long disrupted days and substantial sections where 24-hour rhythmicity was observable. There was a bimodal distribution of sleep onset and a clustering around the «main sleep gate» (2h00-4h00) and the «secondary sleep gate» (14h00-18h00). Almost no sleep episodes were initiated around the «forbidden zone for sleep» namely, around 23h00 (Figure 6). Other cases of patients with introvert personality traits have been reported and responded to antidepressant therapy such as Elavil 50 mg taken at bed time (Eastman et al., 1988).

In 1983, Kamgar-Parsi and colleagues described the case study of a young man who developed an hypernychthemeral sleep-wake syndrome after a stressful chess tournament associated with migraines and sleep disruption. Following the tournament, the patient was unable to get up at 7h30 and missed all his morning classes of the semester. Before this episode, he was regularly sleeping from 23:30 to 7:30. Delayed chronotherapy successfully reentrained him to a socially acceptable schedule but he tended to drift back to his delayed position. His actigraphic data revealed a longer than 24-hour sleep-wake cycle when he was free to do so, but overall he was able to maintain a regular 24-hour schedule although at late times. Again, the clinical picture is more suggestive of a DSPS than a hypernychthemeral syndrome. It was found that his TSH was elevated with normal T3 and T4 concentrations. Because of the high incidence of B12 deficiency in patients with thyroid disease, he decided to self-medicate himself with B12 supplements (up to 0.2 mg/day taken at waketime). No B12 dosage was done prior to treatment. The patient reported an improvement in sleep quality and claimed that B12 supplements helped him to maintain a regular 24-hour sleep-wake cycle. A tendency to relapse to a 25-hour rhythm was reported when the B12 was stopped. It is possible that the chronotherapy used for his DSPS could have worsened his sleep-wake cycle disturbances and led him to live on 25-hour “days”.

A few cases have been reported following traumatic brain injury or in brain damaged children (Okawa et al., 1986; Palm et al., 1991). For instance, Okawa and colleagues (1981) reported the case of a severely brain-damaged 12 y.o. boy with an apparent non-24-hour sleep-wake syndrome. His sleep disturbances appeared to cycle every 10-15 days with no obvious periodic changes in his cortisol rhythm. Sleep structure was substantially disrupted and no sleep spindles or K-complexes were observed on serial polysomnographic recordings. However, this case is unclear since the analysis of his sleep-wake cycle shows a rather consistent 24-hour rhythm with some periods of desynchronisation.

Epidemiology

Non-24-hour sleep-wake syndrome is extremely uncommon in sighted subjects living under normal conditions. Lack of entrainment is more frequently observed in blind patients or in astronauts and sub-mariners living under artificial light-dark cycles (Kennaway et al., 1991).

It can also be associated with psychiatric conditions such as schizoid or avoidant personality disorders. The incidence of sleep-wake disturbances in blind patients is apparently 5 times that observed in healthy subjects and about 76% of blind patients complain of some sleep-wake cycle disturbances (Miles et al., 1977b; Wagner, 1996). It is estimated that between 17 to 50% of blind patients have free-running circadian rhythms (Sack et al., 1992; Leger et al., 1996).

Positive diagnosis

Patients with non-24-hour sleep-wake syndrome often report irregular sleep-wake cycles and periodic insomnia mixed with daytime sleepiness. The condition may go unrecognized for several years as apparent periods of successful treatment with large doses of hypnotics can occur in a recurrent fashion (ICSD, 2001). In the disturbed periods, the patient suffers from severe sleep-onset insomnia and difficulty awakening in the morning. Sleep onset tends to be delayed by 1-2 hours from one day to the other. The sleep-wake cycle disturbances must have been present for at least 6 weeks and shouldn't be better explained by another intrinsic sleep disorder. It can be intrinsic if abnormal circadian mechanisms or entrainment are suspected or extrinsic if socially or environmentally induced. A sleep-wake log and wrist actigraphy monitoring for several consecutive weeks (or even months) is suggested to confirm the diagnosis. This will reveal longer than 24-hour rest-activity cycles that may be interrupted by periods of relative coordination to the 24-hour day. Periods of long days with 24-40 hours without sleep followed by 14-24 hours of uninterrupted sleep may also occur (Wagner, 1990; Uchiyama et al., 1996). Relative coordination and long sleep-wake cycle have been initially observed in healthy individuals kept for months in time free environments and undergoing a phenomenon known as spontaneous desynchronisation. Serial polysomnographic recordings are required to rule out intrinsic sleep disorders and to confirm the cyclical nature of the disturbance. If these recordings are planned at the same clock time, they will reveal a pattern of cyclic sleep disruption. Sighted individuals should also undergo a neurological evaluation with neuroimaging of the suprasellar region (Wagner, 1990; Mahowald et al., 1999).

Pathophysiology

It has been proposed that in sighted individuals, the hypernychthemeral syndrome might be a more severe form of DSPS (Weitzman et al., 1981). Indeed, some cases of DSPS have converted to a non-24-hour sleep-wake syndrome after chronotherapy on a 27-hour day (Kamgar-Parsi et al., 1983; Oren et al., 2001). Animal studies suggest that the hypernychthemeral syndrome can occur as a physiological aftereffect of lengthening the rest-activity cycle (Pittendrigh et al., 1976). This could increase the endogenous circadian period until the 24-hour days falls outside of the new range of entrainment. It is interesting to note that several of the DSPS patients stated that they found themselves going to bed later from one night to the other (Weitzman et al., 1981). A non-24-hour sleep-wake syndrome could thus be seen as a late complication of a sleep disturbance in which the patient deliberately decides to go to bed later to increase his sleepiness and ability to fall asleep (Kamgar-Parsi et al., 1983). In DSPS, a 1-2 hour increase of the waking episode

might induce a tendency to delay sleep onset simulating an hypernychthemeral pattern for short periods of time. The difference between both syndromes may also depend on the ability to phase advance, with greater impairments seen in the hypernychthemeral syndrome. Moreover, the maintenance of a greater-than-24-hour day often worsens the tendency to delay since the patient is exposed to light and darkness at times that favor further phase delays. The weakening of social time cues has been implicated (Wollman et al., 1986) and this could play a role in some patients with personality disorders, if they attempt to minimize social interactions. Studies have also been carried out in people living in Antarctica. When free to choose their own sleep times, humans can present free-running melatonin, cortisol and sleep rhythms (Kennaway et al., 1991). However, they are able to entrain to a 24-hour schedule if they keep regular bedtimes and waketimes (Griffiths et al., 1986). In blind patients, the free-running rhythms of core body temperature, subjective alertness, urinary electrolytes, cortisol, and melatonin (Miles et al., 1977a; Nakagawa et al., 1992; Klein et al., 1993; Sack et al., 1992; Arendt et al., 1988) are presumed to result from an inability to respond to the light-dark cycle as a circadian synchronizer. No substantial reduction of nocturnal melatonin secretion was observed with exposure to light of 500 or 1,000 lux in a sighted 41 y.o. man with hypernychthemeral syndrome (McArthur et al., 1996). These results suggest that a reduced sensitivity of the human circadian system to light could contribute to this syndrome.

Treatment

In children, non-24-hour sleep-wake schedules can be successfully treated by non-pharmacological approaches. For instance, Ferber et Boyle (1983) reported the case of a 11 month old girl whose parents let her set her sleep-wake cycle on a 25-hour schedule. Her sleep schedule normalized with regular feeding and parental interactions. In adults, the treatment of non 24-hour sleep-wake syndrome is much more difficult and once entrainment is achieved, relapses are frequent. Very large doses of hypnotics and stimulants have been tried but the results alternate between efficacy and progressive loss of efficacy (Wagner, 1990). Exogenous melatonin 0.5-6 mg administered per os in the evening has been successfully used to entrain the non-24-hour sleep-wake cycle of a retarded boy (Palm et al., 1991), and the free-running rhythms of a sighted man (McArthur et al., 1996) and several blind patients (Arendt et al., 1988; Sack et al., 1991; Palm et al., 1997; Lapierre et al., 1995; Sarrafzadeh et al., 1990). In one blind man, exogenous melatonin was able to stabilise the sleep-wake cycle but cortisol and temperature rhythms were still free-running (Folkard et al., 1990). These results suggest that the therapeutic efficacy of exogenous melatonin could result from an action on the rest-activity cycle rather than a direct chronobiotic effect on the endogenous circadian system. Eastman and colleagues (1988) published the case of a man who had been free-running since high school. He was described as introverted and resistant to any psychological evaluation. His sleep schedule was temporarily stabilized on Elavil 50 mg taken at bed time for about 3 months. Exposure to bright light for 2-3 hours upon awakening also appeared to stop his free-running pattern although a small drift of a few minutes per day was reported. It is Kamgar-Parsi and colleagues who reported in 1983 the first successful trial of a non-24h sleep-wake syndrome with B12 supplement. Since then other successful treatment cases have been reported

(Okawa et al., 1990; Ohta et al., 1991), although it still remains unclear whether this success is due to a placebo effect or to a physiological action of unknown mechanisms.

Irregular sleep-wake pattern

Historical Background

Irregular sleep-wake pattern (ISWP) is more likely found in nursing homes and demented populations (Okawa et al., 1991; Uchida et al., 1996). For instance, a progressive and increasing disruption of the sleep-wake cycle was reported in patients with senile dementia of Alzheimer type (Vitiello et al., 1990) (Figure 7). In these patients, progressive disruption of SWS, REM sleep, sleep efficiency, increased nightmares, and daytime napping is observed. In ISWP, total sleep time per 24-hour day is about normal and consists of 3-4 bouts of sleep lasting 4 hours or less each day. Disrupted circadian rhythms of body temperature, melatonin, or cortisol have been reported in demented patients or in severely brain-damaged patients. A few cases of ISWP were described in cognitively intact patients with several years of prolonged bedrest (Mishima et al., 1999; Uchida et al., 1996; Satlin et al., 1992; Wagner, 1996) but results vary greatly between studies. Irregular sleep patterns were also reported in patients with severe congenital, developmental or degenerative brain dysfunction (Wagner, 1990).

Epidemiology

The epidemiology of ISWP or its sex prevalence is unknown (ICSD, 2001). It is most frequently described in patients with neurological conditions such as diffuse brain dysfunction, head injury, hypothalamic lesions or developmental disabilities (Mahowald et al., 1999).

Positive diagnosis

A diagnosis of ISWP is made when there are more than three sleep episodes per 24-hour day. The condition must be present for at least 3 consecutive months and is associated with chronic insomnia and daytime sleepiness. The sleep-wake cycle is irregular and disorganized, although the total amount of sleep per day is often normal. Extended polysomnographic recordings (e.g. for 72 hours), in the presence of conventional environmental cues, shows irregular periods of sleep with bouts of 2-3 hours (Allen et al., 1987; Okawa et al., 1986). The overt rhythmicity of circadian markers such as that of core body temperature and melatonin secretion can be disrupted by the disorganized sleep-wake pattern (Touitou et al., 1982).

Pathophysiology

It is possible to create an animal model of ISWP by increasing the photoperiod by about 30 minutes each week (Delagrange et al., 1997; Armstrong, 1999). The rest-activity cycle becomes unstable and disrupted when the light/dark ratio reaches 19 hours/5hours. In demented patients, a reduction of light exposure rather than an extension of the photoperiod was hypothesized to contribute to the appearance of ISWP. In these patients, it was

proposed that a substantial reduction of light exposure in nursing homes or reduced retinal sensitivity to light with age could lead to disrupted sleep patterns and nocturnal wandering (Campbell et al., 1988; Armstrong, 1999). Degenerative brain lesions affecting the SCN or brain areas involved in sleep-wake regulation could also play a role in the appearance of ISWP in demented patients (Swaab et al., 1985; Cohen et al., 1991). In cognitively intact patients, daytime napping and irregular sleep patterns appear principally as a disorder of sleep hygiene (Richardson et al., 1996).

Treatment

ISWP is typically very difficult to treat (Wagner, 1990). Non-pharmacological approaches should aim at increasing the regularity of environmental synchronizers. These consist of regular activities such as meals, outdoor activities and social interactions. Sleep restrictions to nighttime hours is encouraged to help consolidate the main sleep episode (Okawa et al., 1991; Wagner, 1996). Exposure to bright light, either in the morning (Mishima et al., 1994) or in the evening (Satlin et al., 1992) can reduce nocturnal agitation and improve nighttime sleep in demented patients. Therapeutic improvement was also reported with exogenous melatonin 2.5-10 mg at bedtime in children resistant to hypnotics (Jan et al., 1994). Vitamin B12 was tried successfully for ISWP, although a placebo effect is plausible (Okawa et al., 1997).

References

Allen, R., Rosenthal, N., Joseph-Vanderpoll, J.R., Nadeau, J., Kelly, K., Schulz, P., & Souetre, E. (1989). Delayed sleep phase syndrome: polysomnographic characteristics. Sleep Research, 18, 133-133.

Allen, S.R., Seiler, W.O., Stahelin, H.B., & Spiegel, R. (1987). Seventy-two hour polygraphic and behavioral recordings of wakefulness and sleep in a hospital geriatric unit: Comparison between demented and nondemented patients. Sleep, 10(2), 143-159.

Alvarez, B., Dahlitz, M.J., Vignau, J., & Parkes, J.D. (1992). The delayed sleep phase syndrome: clinical and investigative findings in 14 subjects. Journal of Neurology, Neurosurgery & Psychiatry, 55, 665-670.

Aoki, H., Ozeki, Y., & Yamada, N. (2001). Hypersensitivity of melatonin suppression in response to light in patients with delayed sleep phase syndrome. Chronobiology International, 18(2), 263-271.

Arendt, J., Aldhous, M., & Wright, J. (1988). Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. Lancet, 2(1), 772-773.

Armstrong, S.M. (1999). Melatonin as a chronobiotic for circadian insomnia. Clinical observations and animal models. Advances in Experimental Medicine & Biology, 283-297.

Armstrong, S.M., McNulty, O.M., Guardiola-Lemaitre, B., & Redman, J.R. (1993). Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). Pharmacology, biochemistry and behavior, 46, 45-49.

Baker, S.K., & Phyllis, C.Z. (2001). Circadian disorders of the sleep-wake cycle. In: M. H. Kryger, T. Roth, & W. C. Dement (Eds.), Principles and practice of sleep medicine. (pp. 606-614). Philadelphia, Pennsylvania, U.S.A.: W.B. Saunders Company.

Billiard, M., Verge, M., Aldaz, C., Carlander, B., Touchon, J., & Besset, A. (1993a). A case of advanced-sleep phase syndrome. Sleep Research, 22, 109

Billiard, M., Vergé, M., Touchon, J., Carlander, B., & Besset, A. (1993b). Delayed sleep phase syndrome: subjective and objective data chronotherapy and follow-up. Sleep Research, 22, 172-172.

Bixler, E.O., Kales, A., Soldatos, C.R., Kales, J.D., & Healey, S. (1979). Prevalence of sleep disorders in the Los Angeles metropolitan area. American Journal of Psychiatry, 136(10), 1257-1262.

Boivin, D.B., Duffy, J.F., Kronauer, R.E., & Czeisler, C.A. (1996). Dose-response relationships for resetting of human circadian clock by light. Nature, 379(6565), 540-542.

Buysse, D.J., Reynolds III, C.F., Monk, T.H., Hoch, C.C., Yeager, A.L., & Kupfer, D.J. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh sleep quality index (PSQI). Sleep, 14(4), 331-338.

Campbell, S.S., Dawson, D., & Anderson, M.W. (1993). Alleviation of sleep maintenance insomnia with timed exposure to bright light. Journal of the American Geriatric Society, 41, 829-836.

Campbell, S.S., Kripke, D.F., Gillin, J.C., & Hrubovcak, J.C. (1988). Exposure to light in healthy elderly subjects and Alzheimer's patients. Physiology & Behavior, 42(2), 141-144.

Carrier, J., Monk, T.H., Buysse, D.J., & Kupfer, D.J. Sleep and Morningness-Eveningness in the "middle" years of life (20y-59y). Journal of Sleep Research, 6(4), 230-237.

Carskadon, M.A., Labyak, S.E., Acebo, C., & Seifer, R. (1999). Intrinsic circadian period of adolescent humans measured in conditions of forced desynchrony. Neuroscience Letters, 260(2), 129-132.

Cohen, R.A., & Elliott Albers, H. (1991). Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: A case study. Neurology, 41, 726-729.

Coleman, R.M. (1983). Diagnosis, treatment, and follow-up of about 8,000 sleep/wake disorder patients. In: C. Guilleminault & E. Lugaresi (Eds.), Sleep/Wake Disorders: Natural history, epidemiology and long term evolution. (pp. 87-97). New York: Raven press.

Czeisler, C.A., Allan, J.S., Strogatz, S.H., et al. (1986). Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science, 233, 667-671.

Czeisler, C.A., Kronauer, R.E., Allan, J.S., Duffy, J.F., Jewett, M.E., Brown, E.N., & Ronda, J.M. (1989). Bright light induction of strong (Type 0) resetting of the human circadian pacemaker. Science, 244, 1328-1333.

Czeisler, C.A., Dumont, M., Duffy, J.F., et al. (1992). Association of sleep-wake habits in older people with changes in output of circadian pacemaker. Lancet, 340, 933-936.

Czeisler, C.A., Moore-Ede, M.C., & Coleman, R.M. (1983). Resetting circadian clocks: Applications to sleep disorders medicine and occupational health. In: C.

Guilleminault & E. Lugaresi (Eds.), Sleep/Wake Disorders: Natural History, Epidemiology, and Long- Term Evolution. (pp. 243-260). New York: Raven Press.

Czeisler, C.A., & Richardson, G.S. (1991). Detection and assessment of insomnia. Clinical Therapeutics, 13, 663-679.

Dagan, Y., Sela, H., Omer, H., Hallis, D., & Dar, R. (1996). High prevalence of personality disorders among circadian rhythm sleep disorders (CRSD) patients. Journal of Psychosomatic Research, 41(4), 357-363.

Dagan, Y., Stein, D., Steinbock, M., Yovel, I., & Hallis, D. (1998). Frequency of delayed sleep phase syndrome among hospitalized adolescent psychiatric patients. Journal of Psychosomatic Research, 45(1), 15-20.

Dagan, Y., Tzischinsky, O., & Lavie, P. (1991). Sunlight treatment for delayed sleep-phase syndrome: Case report. Sleep Research, 20, 451

Dagan, Y., Yovel, I., Hallis, D., Eisenstein, M., & Raichik, I. (1998). Evaluating the role of melatonin in the long-term treatment of delayed sleep phase syndrome (DSPS). Chronobiology International, 15(2), 181-190.

Dahlitz, M., Alvarez, B., Vignau, J., English, J., Arendt, J., & Parkes, J.D. (1991). Delayed sleep phase syndrome response to melatonin. Lancet, 337, 1121-1124.

deBeck, T.W. (1990). Delayed sleep phase syndrome - criminal offense in the military? Military Medicine, 155(1:14), 14-15.

Delagrange, P., & Guardiola-Lemaitre, B. (1997). Melatonin, its receptors, and relationships with biological rhythm disorders. Clinical Neuropharmacology, 20(6), 482-510.

Dement, W.C., Miles, L.E., & Carskadon, M.A. (1982). "White paper" on sleep and aging. Journal of the American Geriatric Society, 30, 25-50.

Duffy, J.F., Dijk, D.J., Hall, E.F., & Czeisler, C.A. (1999a). Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. Journal of Investigative Medecine, 47(3), 141-150.

Duffy, J.F., Rimmer, D.W., Silva, E.J., & Czeisler, C.A. (1999b). Correlation of intrinsic circadian period with morningness-eveningness in young men. Sleep, 22(Supplement), S92-S92

Eastman, C.I., Anagnopoulos, C.A., & Cartwright, R.D. (1988). Can bight light entrain a free-runner? Sleep Research, 17, 372-372.

Ebihara, S., Mano, N., Kurono, N., Komuro, G., & Yoshimura, T. (1996). Vitamin B12 affects non-photic entrainment of circadian locomotor activity rhythms in mice. Brain Research, 727(1-2), 31-39.

Eliott, A.L., Mills, J.N., & Waterhouse, J.M. (1970). A man with too long a day. Proceedings of the Physiological Society, 30-31.

Ferber, R., & Boyle, M.P. (1983). Persistence of a free-running sleep-wake rhythm in a one year old girl. Sleep Research, 12, 364

Folkard, S., Arendt, J., Aldhous, M., & Kennett, H. (1990). Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. Neuroscience Letters, 113, 193-198.

Fookson, J.E., Kronauer, R.E., Weitzman, E.D., Monk, T.H., Moline, M.L., & Hoey, E. (1984). Induction of insomnia on a non-24 hour sleep-wake schedule. Sleep Research, 13, 220

Giedke, H., Engelmann, W., & Reinhard, P. (1983). Free-running circadian rest-activity cycle in a normal environment. A case study. Sleep Research, 12, 365-365.

Griffiths, P.A., Folkard, S., Bojkowski, C., English, J., & Arendt, J. (1986). Persistant 24-h variations of urinary 6-hydroxy melatonin sulphate and cortisol in Antartica. Experientia, 42, 430-432.

Honma, K., Kohsaka, M., Fukuda, N., Morita, N., & Honma, S. (1992). Effects of vitamin B12 on plasma melatonin rhythm in humans: increased light sensitivity phase-advances the circadian clock? Experientia, 48, 716-720.

Ito, A., Ando, K., Hayakawa, T., Iwata, T., Kayukawa, Y., Ohta, T., & Kasahara, Y. (1993). Long-Term Course of Adult Patients with Delayed Sleep Phase Syndrome. The Japanese Journal of Psychiatry and Neurology, 47(3), 563-567.

Jan, J.E., Espezel, H., & Appleton, R.E. (1994). The treatment of sleep disorders with melatonin. Developmental Medicine & Child Neurology, 36, 97-107.

Joseph-Vanderpool, J.R., Kelly, K.G., Schulz, P.M., Allen, R., Souetre, E., & Rosenthal, N.E. (1988). Delayed sleep phase syndrome revisited: Preliminary effects of light and triazolam. Sleep Research, 17, 381-381.

Joseph-Vanderpool, J.R., Rosenthal, N.E., Levendosky, A.A., Johnston, S.H., Allen, R., Kelly, K.A., Souetre, E., Schulz, P.M., & Starz, B.K. (1989). Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep Research, 18, 422-422.

Kamgar-Parsi, B., Wehr, T.A., & Gillin, J.C. (1983). Successful treatment of human non-24-hour sleep-wake syndrome. Sleep, 6(3), 257-264.

Kennaway, D.J., & Van Dorp, C.F. (1991). Free-running rhythms of melatonin, cortisol, electrolytes, and sleep in humans in Antarctica. American Journal of Physiology, 260, R1137-R1144

Kirmil-Gray, K., Eagleston, J.R., Gibson, E., & Thoresen, C.E. (1984). Sleep disturbance in adolescents: sleep quality, sleep habits, beliefs about sleep, and daytime functioning. Journal of Youth and Adolescence, 13(5), 375-384.

Klein, T., Martens, H., Dijk, D.J., Kronauer, R.E., Seely, E.W., & Czeisler, C.A. (1993). Circadian sleep regulation in the absence of light perception: chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep-wake schedule. Sleep, 16(4), 333-343.

Kokkoris, C.P., Weitzman, E.D., Pollak, C.P., Spielman, A.J., Czeisler, C.A., & Bradlow, H. (1978). Long-term ambulatory temperature monitoring in a subject with a hypernychthemeral sleep-wake cycle disturbance. Sleep, 1, 177-190.

Lack, L., & Wright, H. (1993). The effect of evening bright light in delaying the circadian rhythms and lengthening the sleep of early morning awakening insomniacs. Sleep, 16(5), 436-443.

Lack, L.C. (1986). Delayed sleep and sleep loss in university students. Journal of American College Health, 35, 105-110.

Lapierre, O., & Dumont, M. (1995). Melatonin treatment of a non-24-hour sleep-wake cycle in a blind retarded child. Biological Psychiatry, 38(2), 119-122.

Leger, D., Guilleminault, C., Defrance, R., Domont, A., & Paillard, M. (1996). Blindness and sleep patterns. Lancet, 348, 830-831.

Lewy, A.J., Ahmed, S., Jackson, J.M.L., & Sack, R.L. (1992). Melatonin shifts human circadian rhythms according to a phase- response curve. Chronobiology International, 9(5), 380-392.

Lewy, A.J., Bauer, V.K., Ahmed, S., et al. (1998). The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiology International, 15(1), 71-83.

Lorrain, D., & Boivin, D.B. (1997). Troubles du sommeil. In: M. Arcand & R. Hébert (Eds.), Précis Pratique de Gériatrie. (pp. 239-258). Sherbrooke: Edisem Inc.

Mahowald, M.W., & Ettinger, M.G. (1999). Circadian Rhythm Disorders. In S. Chokroverty (Ed.), Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects. (pp. 619-634). Boston: Butterworth Heinemann.

McArthur, A.J., Lewy, A.J., & Sack, R.L. (1996). Non-24-hour sleep-wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. Sleep, 19(7), 544-553.

Miles, L.E., Raynal, D.M., & Wilson, M.A. (1977a). Blind man living in normal society has circadian rhythms of 24.9 hours. Science, 198, 421-423.

Miles, L.E., & Wilson, M.A. (1977b). High incidence of cyclic sleep/wake disorders in the blind. Sleep Research, 6, 192-192.

Minors, D.S., Waterhouse, J.M., & Wirz-Justice, A. (1991). A human phase-response curve to light. Neuroscience Letters, 133, 36-40.

Mishima, K., Okawa, M., Hishikaa, Y., Hozumi, S., Hori, H., & Takahashi, K. (1994). Morning bright light therapy for sleep and behaviour disorders in elderly patients with dementia. Acta Psychiatrica Scandinavica, 89, 1-7.

Mishima, K., Tozawa, T., Satoh, K., Matsumoto, Y., Hishikawa, Y., & Okawa, M. (1999). Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep-waking. Biological Psychiatry, 45(4), 417-421.

Moldofsky, H., Musisi, S., & Phillipson, E.A. (1986). Treatment of a case of advanced sleep phase syndrome by phase advance chronotherapy. Sleep, 9(1), 61-65.

Monk, T.H., Buysse, D.J., Reynolds III, C.F., Kupfer, D.J., & Houck, P.R. (1995). Circadian temperature rhythms of older people. Experimental Gerontology, 30(5), 455-474.

Morris, M., Lack, L., & Dawson, D. (1990). Sleep-onset insomniacs have delayed temperature rhythms. Sleep, 13(1), 1-14.

Nagtegaal, J.E., Kerkhof, G.A., Smits, M.G., Swart, A.C.W., & Van Der Meer, Y.G. (1997). Traumatic brain injury-associated delayed sleep phase syndrome. Functional Neurology, 12(6), 345-348.

Nakagawa, H., Sack, R.L., & Lewy, A.J. (1992). Sleep propensity free-runs with the temperature, melatonin and cortisol rhythms in a totally blind person. Sleep, 15(4), 330-336.

Ohta, T., Ando, K., Iwata, T., Ozaki, N., et al. (1991). Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12). Sleep, 14(5), 414-418.

Okawa, M., Mishima, K., Hishikawa, Y., Hozumi, S., Hori, H., & Takahashi, K. (1991). Circadian rhythm disorders in sleep-waking and body temperature in elderly patients with dementia and their treatment. Sleep, 14(6), 478-485.

Okawa, M., Mishima, K., Nanami, T., Shimizu, T., Iijima, S., Hishikawa, Y., & Takahashi, K. (1990). Vitamin B12 treatment for sleep-wake rhythm disorders. Sleep, 13(1), 15-23.

Okawa, M., Nanami, T., Wada, T., Shimizu, T., Hishikawa, Y., Sasaki, H., Nagamine, H., & Takahashi, K. (1987). Four congenitally blind children with circadian sleep-wake rhythm disorder. Sleep, 10(2), 101-110.

Okawa, M., Sasaki, H., Nakajima, S., & Takahashi, K. (1981). Altered sleep rhythm: a patient with a 10 to 15 day cycle. Journal of Neurology, 266, 63-71.

Okawa, M., Takahashi, K., Egashira, K., Furuta, H., et al. (1997). Vitamin B12 treatment for delayed sleep phase syndrome: A multi-center double-blind study. Psychiatry and Clinical Neurosciences, 51, 275-279.

Okawa, M., Takahashi, K., & Sasaki, H. (1986). Disturbance of circadian rhythms in severely brain-damaged patients correlated with CT findings. Journal of Neurology, 233, 274-282.

Oldani, A., Ferini-Strambi, L., Zucconi, M., Stankov, B., Fraschini, F., & Smirne, S. (1994). Melatonin and delayed sleep phase syndrome: ambulatory polygraphic evaluation. Neuroreport, 6, 132-134.

Oren, D.A., Turner, E.H., & Wehr, T.A. (1995). Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome. Journal of Neurology, Neurosurgery and Psychiatry, 58, 379-385.

Oren, D.A., & Wehr, T.A. (2001). Hypernychthemeral syndrome after chronotherapy for delayed sleep phase syndrome. New England Journal of Medecine, 327, 1762

Ozaki, N., Iwata, T., Itoh, A., Kogawa, S., hta, T., kada, T., & asahara, Y. (1988). Body temperature monitoring in subjects with delayed sleep phase syndrome. Neuropsychobiology, 20, 174-177.

Ozaki, S., Uchiyama, M., Shirakawa, S., & Okawa, M. (1996). Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. Sleep, 19(1), 36-40.

Palm, L., Blennow, G., & Wetterberg, L. (1991). Correction of non-24-hour sleep/wake cycle by melatonin in a blind retarded boy. Annals of Neurolology, 29, 336-339.

Palm, L., Blennow, G., & Wetterberg, L. (1997). Long term melatonin treatment in blind children and young adults with circadian sleep-wake disturbances. Developmental.Medicine & Child Neurology, 39(5), 319-325.

Patten, S.B., & Lauderdale, W.M. (1992). Delayed sleep phase disorder after traumatic brain injury. Journal of the American Academy of Child and Adolescent Psychiatry, 31(1), 100-102.

Pittendrigh, C.S., & Daan, S. (1976). A functional analysis of circadian pacemakers in nocturnal rodents I. the stability and lability of spontaneous frequency. Journal of Comparative Physiology A, 106, 223-252.

Price, V.A., Coates, T.J., Thoresen, C.E., & Grinstead, O.A. (1978). Prevalence and correlates of poor sleep among adolescents. American Journal of Diseases of Children, 132(June), 583-586.

Quinto, C., Gellido, C., Chokroverty, S., & Masdeu, J. (2000). Posttraumatic delayed sleep phase syndrome. Neurology, 54(1), 250-252.

Regestein, Q.R., & Monk, T.H. (1995). Delayed sleep phase syndrome: A review of its clinical aspects. American Journal of Psychiatry, 2, 602-608.

Reyner, A., & Horne, J.A. (1995). Gender- and aging-related differences in sleep determined by home-recorded sleep logs and actimetry from 400 adults. Sleep, 18(2), 127-134.

Richardson, G.S., & Malin, H.V. (1996). Circadian rhythm sleep disorders: pathophysiology and treatment. Journal of Clinical Neurophysiology, 13(1), 17-31.

Rosenthal, N.E., Joseph-Vanderpool, J.R., Levendosky, et al. (1990). Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep, 13(4), 354-361.

Sack, R.L., & Lewy, A.J. (1997). Melatonin as a chronobiotic: treatment of circadian desynchrony in night workers and the blind. Journal of Biological Rhythms, 12(6), 595-603.

Sack, R.L., Lewy, A.J., Blood, M.L., Keith, L.D., & Nakagawa, H. (1992). Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. Journal of Clinical Endocrinology and Metabolism, 75, 127-134.

Sack, R.L., Lewy, A.J., Blood, M.L., Stevenson, J., & Keith, L.D. (1991). Melatonin administration to blind people: Phase advances and entrainment. Journal of Biological Rhythms, 6(3), 249-261.

Sarrafzadeh, A., Wirz-Justice, A., Arendt, J., & English, J. (1990). Melatonin stabilises sleep onset in a blind man. In: J. Horne (Ed.), Sleep '90. (pp. 51-54). Bochum: Pontenagel Press.

Satlin, A., Volicer, L., Ross, V., Herz, L., & Campbell, S. (1992). Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. American Journal of Psychiatry, 149, 1028-1032.

Schrader, H., Bovim, G., & Sand, T. (1996). Depression in the delayed sleep phase syndrome. American Journal of Psychiatry, 153(9), 1238-1238.

Singer, C.M., & Lewy, A.J. (1989). Case report: Use of the dim light melatonin onset in the treatment of ASPS with bright light. Sleep Research, 18, 445

Strogatz, S.H., Kronauer, R.E., & Czeisler, C.A. (1987). Circadian pacemaker interferes with sleep onset at specific times each day: Role in insomnia. American Journal of Physiology, 253, R172-R178

Swaab, D.F., Fliers, E., & Partiman, T.S. (1985). The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Research, 342, 37-44.

Takahashi, K., Okawa, M., Matsumoto, M., Mishima, K., et al. (1999). Double-blind test on the efficacy of methylcobalamin on sleep-wake rhythm disorders. Psychiatry and Clinical Neurosciences, 53, 211-213.

The International Classification of Sleep Disorders Revised Diagnostic and Coding Manual (1997 Revised ed.). (2001). Lawrence, Kansas, Allen Press Inc.

Toh, K.L., Jones, C.R., He, Y., Eide, E.J., et al. (2001). An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science, 291, 1040-1043.

Touitou, Y., Sulon, J., Bogdan, A., et al. (1982). Adrenal circadian system in young and elderly human subjects: a comparative study. Journal of Endocrinology, 93, 201-210.

Uchida, K., Okamoto, N., Ohara, K., & Morita, Y. (1996). Daily rhythm of serum melatonin in patients with dementia of the degenerate type. Brain Research, 717, 154-159.

Uchiyama, M., Okawa, M., Ozaki, S., Shirakawa, S., & Takahashi, K. (1996). Delayed phase jumps of sleep onset in a patient with non-24-hour sleep-wake syndrome. Sleep, 19(8), 637-640.

Vitiello, M.V., & Prinz, P.N. (1990). Sleep/wake patterns and sleep disorders in Alzheimer's disease. In: M. J. Thorpy (Ed.), Handbook of Sleep Disorders. (pp. 703-718). New York: Marcel Dekker.

Wagner, D.R. (1990). Circadian rhythm sleep disorders. In: M. J. Thorpy (Ed.), Handbook of Sleep Disorders. (pp. 493-527). New York: Marcel Dekker.

Wagner, D.R. (1996). Disorders of the circadian sleep-wake cycle. Neurologic clinics, 14(3), 651-670.

Weber, A.L., Cary, M.S., Connor, N., & Keyes, P. (1980). Human non-24-hour sleep - wake cycles in an everyday environment. Sleep, 2(3), 347-354.

Weitzman, E.D. (1981). Sleep and its disorders. Annual Review of Neuroscience, 4, 381-417.

Weitzman, E.D., Czeisler, C., Coleman, R., Dement, W., et al. (1979). Delayed sleep phase syndrome: A biological rhythms sleep disorder. Sleep Research, 8, 221

Weitzman, E.D., Czeisler, C.A., Coleman, R.M., Spielman, A.J., et al. (1981). Delayed sleep phase syndrome: a chronobiologic disorder associated with sleep onset insomnia. Archives of General Psychiatry, 38, 737-746.

Weyerbrock, A., Timmer, J., Hohagen, F., Berger, M., & Bauer, J. (1996). Effects of light and chronotherapy on human circadian rhythms in delayed sleep phase syndrome: cytokines, cortisol, growth hormone, and the sleep-wake cycle. Biological Psychiatry, 40(8), 794-797.

Wollman, M., & Lavie, P. (1986). Hypernychthemeral sleep-wake cycle: Some hidden regularities. Sleep, 9(2), 324-334.