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RESTORATION OF DETECTABLE MELATONIN AFTER ENTRAINMENT TO A 24-HOUR SCHEDULE IN A 'FREE-RUNNING' MAN

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SUMMARY

We evaluated a 37-year-old male with a non-24-h sleep–wake disorder. His environment gave him little exposure to bright light. Circadian profiles of temperature, melatonin, thyrotropin, cortisol and testosterone were obtained along with endocrine challenges of the thyroid, adrenal, growth hormone and gonadal axes. Multiple endocrine abnormalities were detected. Testosterone was low and nocturnal thyrotropin levels were erratic. Serum melatonin was undetectable throughout the day and night on multiple occasions, and responses to infusions of TRH, GnRH and GRF-44 were abnormal. Responses to CRH infusion were normal. The patient was successfully entrained to a 24-h schedule by daily exposure to 2500 lux light from 0700h to 0900h, avoidance of light (by wearing dark goggles) from 1800h to 2300h, and strict enforcement of a dark environment from 2300h to 0700h. After entrainment, a normal pattern of nocturnal melatonin secretion was found. GH response to GRF-44 also normalized, although abnormal responses to TRH and GnRH persisted. This case raises the possibility that a complex interaction of light exposure with the circadian system can reversibly suspend pineal gland secretion of melatonin indefinitely. It also suggests that circadian rhythm disorders be considered in the differential diagnosis of abnormal endocrine function. Published by Elsevier Science Ltd.

Keywords—Hypernychthemeral; Sleep; Light; Circadian rhythms; Melatonin; Testosterone.

'What hath night to do with sleep?'
John Milton, Comus (1634), line 122.

INTRODUCTION

Little is known of the effects of disorders of the sleep–wake cycle on endocrine function. We present a detailed case-report of a patient who was not entrained to the 24-h day–night schedule, but instead 'free ran,' going to bed and arising about 1 h later each day. Consequently, his sleep period gradually drifted completely around the clock, over and over

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again. Extensive endocrinological investigations revealed that he had significant associated endocrine abnormalities. Furthermore, these abnormalities were partially corrected by treatment of the sleep–wake disorder with light and dark therapy. Light therapy alone has been used as a helpful treatment for this syndrome in at least two previously published reports (Eastman et al., 1988; Hoban et al., 1989)

This 37-year-old male presented to us with a 9-year history of hypernychthemeral syndrome (Elliott et al., 1971; Kokkoris et al., 1978), a disorder in which patients are unable to entrain their sleep–wake cycle and other circadian rhythms to the 24-h day. Although its cause is unknown, this debilitating syndrome has been reported in some cases, including this one, to be a sequela of delayed-sleep-phase-syndrome (DSPS), another sleep–wake disorder in which patients are unable to fall asleep until quite late and have difficulty arising in the morning (Oren & Wehr, 1992; Weitzman et al., 1981).

PAST HISTORY

Childhood

The patient reported a lifelong history of difficulty falling asleep until late at night and a history of chronic fatigue since his early teen years. He was the product of a difficult forceps delivery, after which a bruise was noted above his right eye. During infancy he was often awake during 'naptimes' and would quietly stay up late even when placed in his crib at a consistent time for sleep. At the age of 3 he was noted to have esotropia following a high fever. Resultant strabismic amblyopia in his right eye caused impairment of his depth perception. At the age of 9 he had right ocular surgery to correct the esotropia. While in college, he developed DSPS. His daily schedule worsened so that by the age of 25 he typically slept from 0600h to 1400h daily. Treating himself with chronotherapy at age 28 for the DSPS (Czeisler et al., 1979), he delayed his bedtime progressively later each day, hoping gradually to shift his sleep period until he was sleeping during normal hours. The delaying pattern progressed beyond his control, as he noticed a persistent subjective morning 'sluggishness'. He thereby developed hypernychthemeral syndrome, manifested by a 25.25- to 25.5-h sleep–wake schedule. (See Fig. 1.) Diagnostic SCID of Axis I DSM-III-R disorders showed no evidence of any non-sleep–wake disorder (Spitzer et al., 1989). Clinical evaluation by a psychiatrist provided no evidence of a personality disorder. Although he did not meet criteria for major depressive disorder, his persistent fatigue and inability to entrain to a 24-h schedule frequently left him dysphoric. There was no family history of a sleep disorder.

The patient was a graduate of bachelor's and master's degree programs from internationally-recognized universities. He was unmarried, lived on the lower level of his parents' suburban split-level house, and largely withdrew from social interactions, despite having a pleasant and engaging demeanor.

BASELINE EXAM

Results of preliminary laboratory tests

To rule out the possibility that the patient was less sensitive than healthy individuals to dim light, and thus perhaps insensitive to the normal lighting cues that may entrain the circadian pacemaker (Wehr, 1991), we assessed his psychophysical adaptation to dim light

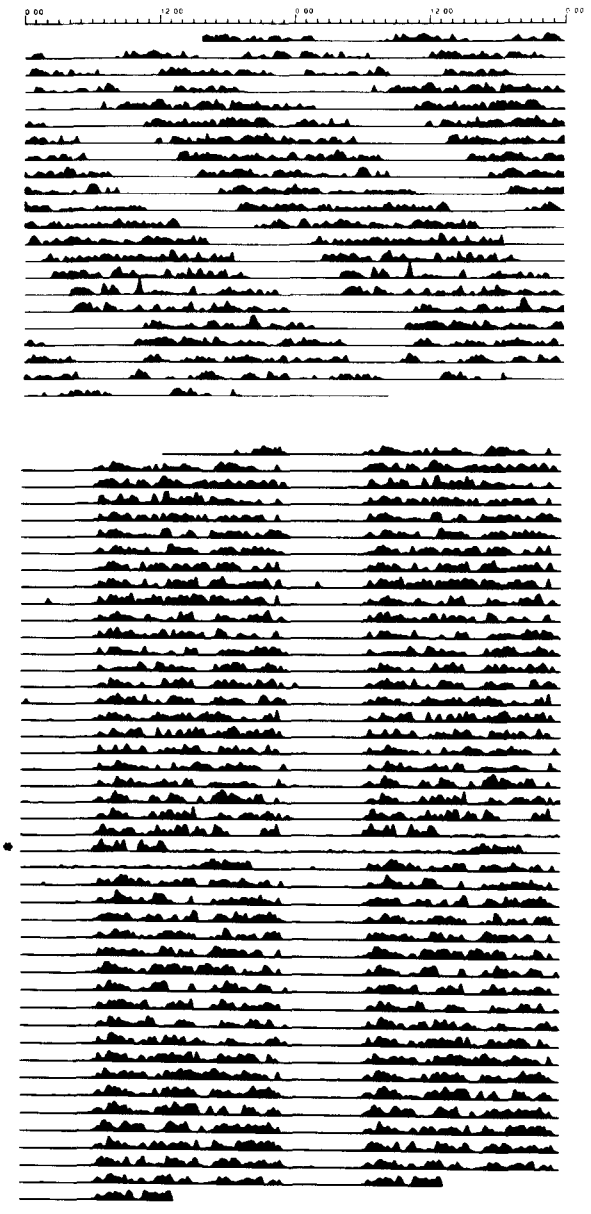

Fig. 1. Raster plots of patient's actigraphic record of activity (periods of motion in dark and periods of sleep in white), double-graphed so that each horizontal line represents a 48-h period. Each subsequent line begins 24 h after the onset of the line it follows. Upper; during free-running state. Lower; during treated state. The line with an asterisk marks a 24-h period during which a 'constant routine' protocol was conducted.

(Békésy, 1947; Gunkel & Bornschein, 1957; Oren et al., 1991). Dark adaptation was within normal limits. Because of prior reports indicating successful treatment of hypernychthemeral syndrome with cyanocobalamin (Vitamin B12) (Kamgar-Parsi et al., 1983; Okawa et al.,

1991), we measured methyl-malonic acid and homocysteine levels to rule out cobalamin deficiency (Allen et al., 1990). Neither methyl-malonic acid (86 nmol/l) nor homocysteine (5.0 nmol/l) were elevated (GCMS, Robert H. Allen, MD, Denver), arguing against a cobalamin deficiency. Inhibin level was 6.1 U/ml (Nichols Institute, San Juan Capistrano, CA, normal range of 4.0–14.0 U/ml). Brain CT scan showed a prominent left Sylvian fissure and a small, calcified, 3-mm-wide pineal gland. Brain MRI scan showed asymmetric optic nerves, apparently secondary to the amblyopia, optic surgery and/or birth trauma.

Light exposure profile

To determine whether the patient was exposed to an unusual pattern of light that might contribute to his inability to entrain to the 24-h day–night cycle, we used an ambulatory electronic device (Actillume®) (Cole et al., 1995) to monitor the patient's daily exposure to light. Comparison of his median daily light exposure with that of a sample of 12 healthy volunteers from another study (Oren et al., 1994) was striking in that it revealed the relative paucity of light to which the patient exposed himself. From time of arising to bedtime, his average light exposure of 43 lux was very low—less than that seen in any of our volunteers—and his total daily level of light exposure of 817 lux hours was less than that of all but one of our volunteers.

Sleep profile

Overnight sleep electroencephalogram demonstrated a normal sleep architecture during his sleeping hours. The patient slept for 594 min, of which 4% was Stage 1 sleep, 61% was Stage 2 sleep, 8% was Stage 3 sleep, 8% was Stage 4 sleep and 20% was REM sleep. Sleep latency was somewhat long at 38 min, and REM sleep latency was short at 54 min.

METHODS

24-Hour profiles

Because of previous evidence of abnormal thyroid axis function in another patient with hypernychthemeral syndrome (Kamgar-Parsi et al., 1983) and recent evidence documenting that manipulations of the photoperiod (length of daylight exposure) can affect circadian rhythms of several hormones (Wehr et al., 1993), we performed a complete evaluation of circadian hormonal patterns in this subject. In the first pair of studies blood samples were obtained every hour for 26 h in a dimly lit room (< 1 lux) while the patient was permitted to sleep according to his usual routine. Samples were analyzed for levels of melatonin and prolactin. (This was not frequent enough to allow detection of subtle pulsatile secretory abnormalities of prolactin.) In a second pair of studies, the patient was in a sleep-deprived state throughout 26 h in the dim room, consumed small isocaloric meals every 2 h, and had blood samples drawn hourly for analysis of melatonin, TSH and cortisol. Samples for measurement of testosterone were obtained every 6 h, and rectal temperature was monitored throughout. The purpose of this 'constant-routine' protocol was to minimize or distribute evenly the potential masking effects of sleep, posture, exercise, meals and light, which might distort the intrinsic patterns of circadian rhythms (Mills et al., 1978). The first of each pair of these studies was performed at a time when the patient's subjective night was expected to coincide with solar night ('behaviorally in phase'), and the second was performed when the patient's subjective night was expected to coincide with solar daytime ('behaviorally out of phase'). All four of these analyses took place within a 6-week period. Urine was also

collected for analysis of 6-sulfatoxymelatonin over a 3-day period and 24-h analysis of urinary free cortisol when the patient was in phase. On a separate occasion when the patient was in phase, blood samples were obtained every 10 min for 26 h while the patient was permitted to sleep and to use room lights ad libitum. LH pulse signal cluster analysis was then conducted using the 'Cluster Analysis' program of Veldhuis and Johnson (Urban et al., 1989). Between 0800h and 1400h during the procedure, blood samples were also obtained for calculation of bioactive LH levels so that bioactive/immunoactive LH ratios could be calculated (Dufau et al., 1983).

Endocrine challenge tests

While the patient was hypernychthemeral, a series of hypothalamic releasing hormone challenges were each performed on two occasions: once at 0900h when the patient was 'in-phase' and once at 2100h when the patient was 'out-of-phase.' All of the challenges were performed on separate occasions in a dimly-lit (< 1 lux) room. Hypothalamic releasing hormones were administered intravenously over 2 min intervals. Aliquots of 400 μg of thyrotropin-releasing hormone (TRH) were administered and blood was obtained for analysis of TSH, prolactin, triiodothyronine (T3) and tetraiodothyronine (T4). Separately, 25 μg of gonadorelin (GnRH) was administered, and blood was obtained for analysis of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Separately, 1 μg/kg of growth hormone releasing factor (GRF-44) was administered intravenously, and blood samples were obtained for analysis of growth hormone (GH). Separately, on one occasion 1 μg/kg of ovine corticotropin releasing hormone (CRH) was administered intravenously at 2000h, and blood samples were obtained for analysis of corticotropin (ACTH) and cortisol. Separately, in an attempt to stimulate the acute production of serum melatonin, the patient was given 100 mg desipramine orally at 1600h (Franey et al., 1986) and blood samples were then obtained through an intravenous catheter hourly for a 20-h period. The patient was permitted to sleep ad libitum.

Assays

Melatonin and urinary hydroxymelatonin radioimmunoassays were performed by Stockgrand, Ltd (Fraser et al., 1983). The melatonin assay had a detection limit of 5 pg/ml, with intra-assay coefficients of variation of 5.6% to 7.2% and interassay coefficients of variation of 7.6% to 11.8%. The hydroxymelatonin assay had a detection limit of 0.3 ng/ml, with intra-assay coefficients of variation of 3.4% to 5.9% and interassay coefficients of variation of 6.4% to 7.8%. The TSH radioimmunoassay was performed with a kit from Serono Diagnostics with a detection limit of 0.02 μIU/ml. TSH intra-assay coefficients of variation were 1.6% to 2.6% and interassay coefficients of variation were 3.6% to 5.4%. The T3 radioimmunoassay intra-assay coefficients of variation were 2.0% to 3.5% and interassay coefficients of variance were 2.7% to 4.2%. The T4 radioimmunoassay intra-assay coefficients of variation were 2.1% to 3.7% and interassay coefficients of variance were 3.1% to 4.9%. The FSH radioimmunoassay intra-assay coefficients of variation were 2.5% to 4.7% and interassay coefficients of variation were 4.6% to 8.6%. The LH radioimmunoassay intra-assay coefficients of variation were 2.8% to 3.9% and interassay coefficients of variation were 5.0% to 6.2%. The prolactin radioimmunoassay intra-assay coefficients of variation were 2.4% to 3.6% and interassay coefficients of variation were 3.8% to 4.7%. Intra-assay reliability of the cortisol assay was 5.4% and interassay reliability was 14.2%. The TSH radioimmunoassay was performed with a kit from Nichols Institute with a

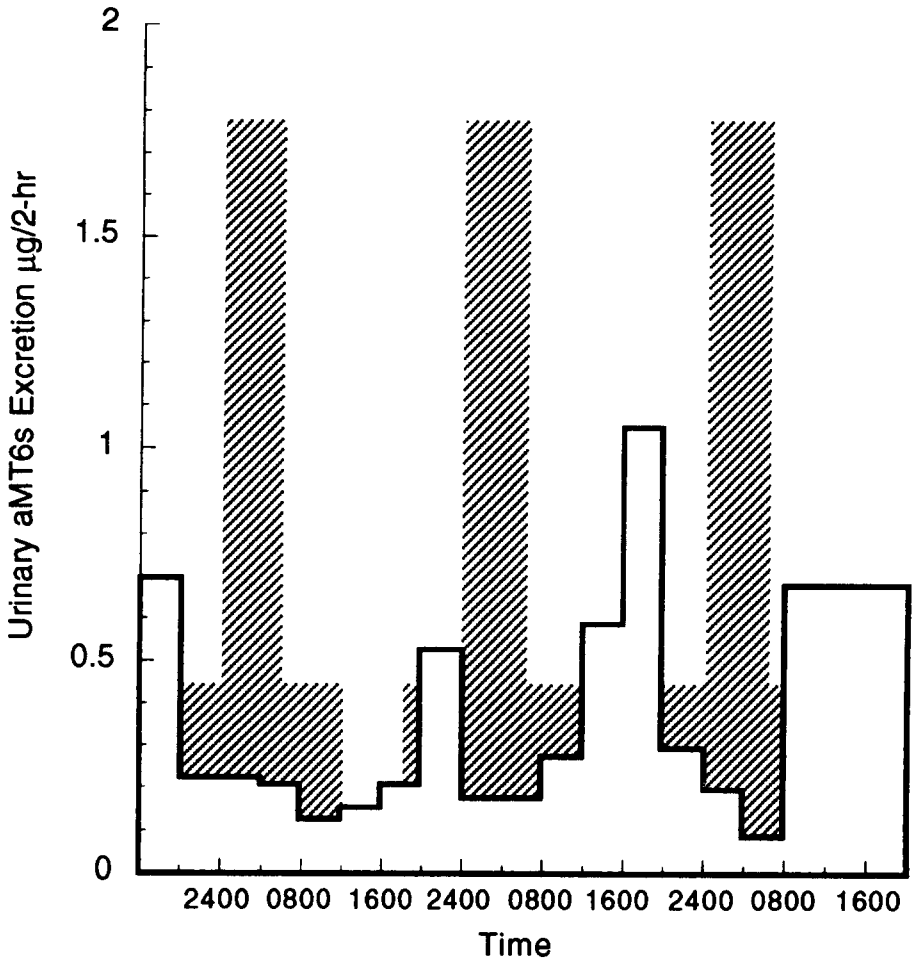

Fig. 2. Urinary 6-sulfatoxymelatonin (μg/2 h interval) in the hypernychthemeral state depicted in white. The shaded background profile depicts excretion profiles of healthy volunteers and is derived from a figure by Arendt et al. (1985).

detection limit of 0.02 mIU/l. Intra-assay reliability of the ACTH assay was 9% and interassay reliability was 20%. The assay had a detection limit of 1.5 pg/ml. The growth hormone radioimmunoassay was performed by Mayo Medical Labs. The assay had a detection limit of 0.1 ng/ml. Intra-assay coefficients of variation were 5.0% and interassay coefficients of variation were 8.0% to 11.6%.

RESULTS

Melatonin

No serum melatonin was detected in any of the samples obtained during any of the four 24-h periods of study. Furthermore, no serum melatonin was detectable in response to acute administration of desipramine. Paradoxically, the 3-day urine sampling showed evidence of

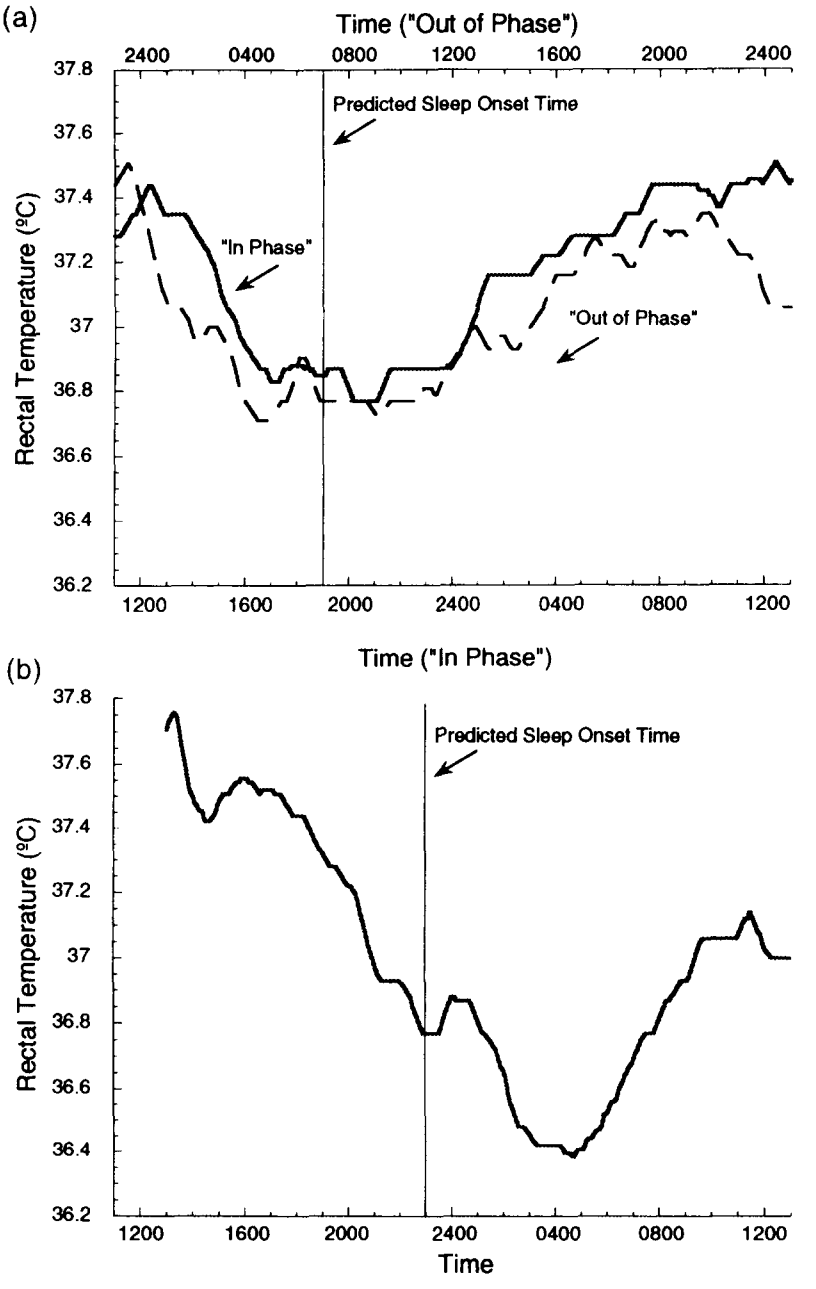

Fig. 3. (a) Hypernychthemeral temperature profile obtained during sleep-deprived constant routines. The solid line represents the 'behaviorally in phase' data and extends from 1100h through 1300h the next day; the dashed line represents the 'behaviorally out of phase' data and extends from 2300h through 0100h 26 h later. Predicted sleep time during the 'in-phase' interval was 1900h to 0300h. Predicted sleep time during the 'out-of-phase' interval was 0700h to 1500h. (b) A 24-h post-treatment temperature profile obtained during sleep-deprived constant routine. Predicted sleep time during this interval was 2300h to 0700h.

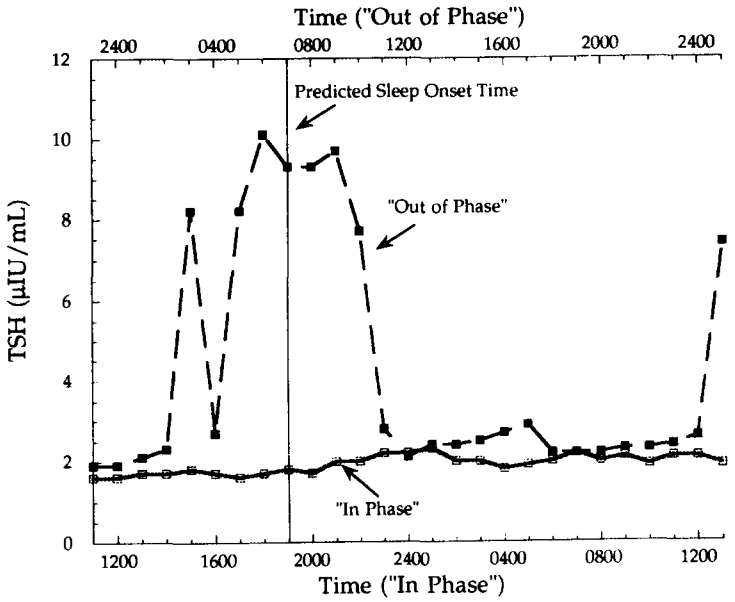

Fig. 4. Hypernychthemeral TSH (μIU/ml) profile obtained during sleep-deprived constant routines. Format as in Fig. 3a.

urinary 6-sulfatoxymelatonin, with an average daily production of 4.3 μg. (See Fig. 2.) This level of urinary 6-sulfatoxymelatonin production placed him in the lowest 15 percentile of a normal sample of subjects whose urinary 6-sulfatoxymelatonin was measured in a different study (Jack Yanovski, personal communication).

Rectal temperature

In both phases of his sleep schedule, the amplitude of the patient's circadian temperature rhythm was low (0.6–0.8°C), and the pattern was unusual in that it was characterized by a decline in temperature several hours before the expected onset of sleep. (See Fig. 3a.)

Hypothalamic–pituitary axis hormones

All prolactin levels were less than 7 ng/ml. During the 'in phase' sleep-deprived study, the patient failed to demonstrate any nocturnal surge of TSH. During the 'out of phase' sleep-deprived study, he had an exaggerated surge of TSH during his subjective night-time (i.e. the middle of the day). (See Fig. 4.) Compared to historically normal controls (Refetoff, 1989), his TSH response to 400 μg intravenous TRH was exaggerated, reaching a plasma peak of 36.4 mIU/l after 30 min. Compared to historically normal controls (Plymate et al., 1989), testosterone levels during both phases of the patient's sleep schedule were consistently low (acrophase 239 ng/dl) and did not differ between the two patterns of his sleep that were studied. Serial testosterone levels obtained between 1000h and 1100h ranged between 144 ng/dl and 198 ng/dl. (Of 13 other males studied under similar conditions, none had a testosterone level less than 226 ng/dl during these hours, and the mean ± SD for that group was 552 ± 210 ng/dl.) His inhibin level was 6.1 U/ml (normal range of 4–14 U/ml). The patient had low baseline FSH levels (below 2 mIU/ml), which were unresponsive to GnRH infusion. Baseline LH levels were low–normal, but responded normally to the infusion of

GnRH. Mean intervals between LH pulses were 248 ± 172 min (normal interval of 56 ± 1.3 min) (Veldhuis, 1991). The maximum bioactive/immunoactive LH ratio observed was 2.1, with the observed ratio mostly below 1 (normal ratio greater than 1) (Dufau et al., 1983). GH responded minimally to stimulation with 1 μg/kg intravenous GRF-44, increasing from 1.1 ng/ml at baseline to 3.0 ng/ml after 60 min. Daily variations in cortisol levels were of normal amplitude, with an atypical circadian pattern suggestive of bimodal secretion. Cortisol and ACTH responses to CRH were normal, as was the 24-h secretion of urinary free cortisol (75 μg).

TREATMENT

Details/light exposure profile

Beginning on a day when we projected that the subject's hypernychthemeral schedule would have him arise at about 0700h, the subject was successfully able to comply with a 24-h schedule with daily use of 2500 lux white light phototherapy from 0700h to 0900h, wearing of dark goggles from 1800h to 2300h daily, and strict enforcement of a totally dark environment from 2300h to 0700h nightly during which he was asked to try to sleep. (See Fig. 1b.) He was asked to avoid any sleep outside 2300h to 0700h except for an optional 'naptime' from 1500h to 1700h daily. Because of complaints of persistent 'sluggishness' despite being on a 24-hour daily schedule for 6 months, the patient was later asked to go to bed at 2200h nightly. On this schedule he reported persistence of the sluggishness, but less need for daytime naps.

Intra-treatment results

All of the previously abnormal hormonal profiles tests were repeated after the patient had been in the light-treated state for at least 8 weeks. The challenge tests were performed at 0900h. In the treated state the patient had a normal serum melatonin profile. (See Fig. 5.) There was a normal amplitude and timing of circadian variation in body temperature. (See Fig. 3b.) The patient's response to TRH in the treated state was essentially identical to that seen while he was hypernychthemeral. Testosterone levels obtained between 1000h and 1100h remained low, ranging between 197 ng/dl and 236 ng/dl. FSH levels were still low in amplitude and unresponsive to GnRH challenge. The GH response to 1 μg/kg intravenous GRF-44 stimulation normalized, increasing from 1.2 ng/ml at baseline to 14.4 ng/ml after 60 min. Circadian cortisol patterns continued to be of normal amplitude, with relatively low levels during the early evening, but the bimodal pattern was lost.

Sleep architecture of one night's sleep during his treatment showed that he slept for 433 min, of which 4% was Stage 1 sleep, 60% was Stage 2 sleep, 6% was Stage 3 sleep, 2% was Stage 4 sleep and 28% was REM sleep. Sleep latency was 22 min and REM sleep latency remained 54 min. A multiple sleep-latency test (Carskadon et al., 1986) showed an average sleep onset time of 6.5 min, with no sleep-onset periods of REM sleep. These results place the patient in a diagnostic 'gray area' with too long a sleep latency time to suggest narcolepsy or other disorders of excessive sleepiness, but too short a sleep latency to be consistent with normal sleep patterns (van den Hoed et al., 1981).

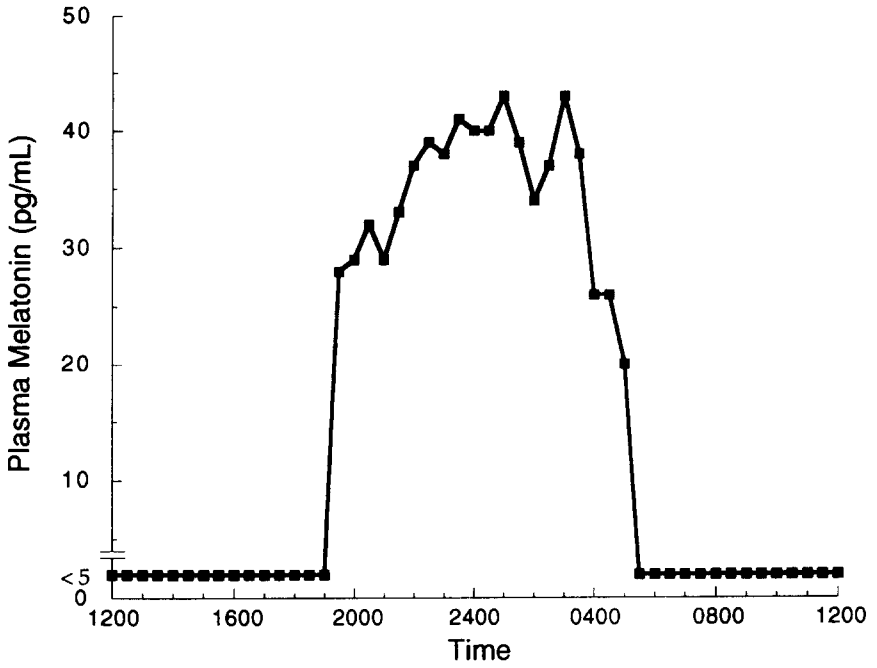

Fig. 5. A 24-h post-treatment melatonin profile obtained during sleep-deprived constant routine. Predicted sleep time during this interval was 2300h to 0700h.

DISCUSSION

This case raises the possibility that a complex interaction of light exposure with the circadian system can reversibly suspend pineal gland secretion of melatonin in humans indefinitely. Seasonally-mediated suspension of nocturnal melatonin production has been documented in lower mammals (Vivien-Roels et al., 1992). This case also raises the possibility that circadian rhythm disorders need to be considered in the differential diagnosis of abnormal endocrine function.

As noted in the study of the first hypernychthemeral patient described in the modern scientific literature (Elliott et al., 1971), our patient's body temperature rhythm was coupled to his sleep–wake cycle. The phase relationship between the temperature and sleep–wake rhythms with sleep onset occurring near the time of the temperature minimum was abnormal, and resembled that observed in healthy individuals whose circadian rhythms free-run in temporal isolation ('cave') experiments (Parkes, 1985). In contrast, following entrainment to a 24-h rhythm, this phase relationship reverted to a normal pattern, with sleep onset occurring several hours before the nightly temperature minimum. Like our previous patient with the syndrome (Kamgar-Parsi et al., 1983), this subject had abnormal thyroid axis function, with elevated serum TSH levels on one occasion and an exaggerated response to TRH stimulation. The hypothalamic–pituitary–gonadal axis of our patient was also markedly abnormal. We do not know if this was caused by an ultradian regulatory disorder, or whether light therapy corrected this problem. Although we did not study our previous patient's gonadal axis, that patient recently reported to us that he currently receives testosterone injections from his internist as a successful treatment for impotence. This may

be of particular import in that one study of male rodents has demonstrated that testosterone is capable of shortening the period of circadian activity rhythm (Daan et al., 1975). One might ask, therefore, if diminished testosterone levels, at least in males, might be associated with unusually long circadian activity rhythm periods. Co-existent abnormalities of the thyroid and gonadal axes, consequently, may possibly be linked to this syndrome.

Explanation of the loss of bimodal cortisol secretion after light treatment must be speculative. Nevertheless, one hypothesis would be that the bimodality reflected the same underlying processes that sometimes allow bimodal sleep patterns in normal humans sleeping during long nights (Wehr et al., 1995). Since melatonin administration can stimulate release of growth hormone (Esposti et al., 1988; Petterborg et al., 1991; Valcavi et al., 1987, 1993), the restoration of a normal growth hormone response to a GRF-44 challenge after the successful treatment of the sleep–wake disorder could be a consequence of the restoration of normal melatonin production. Melatonin has been postulated to act at the level of the hypothalamus by inhibiting endogenous somatostatin release (Valcavi et al., 1993).

The cause of our patient's condition is unknown, although the course of this patient's illness adds further support to earlier suggestions that hypernychthemeral sleep–wake syndrome and delayed sleep-phase syndrome may be manifestations of the same underlying process (Weitzman et al., 1982). A deficiency of melatonin might account for a failure of the body clock to be entrained normally, but we have seen a few other subjects with undetectable serum melatonin who appeared to have normal sleep–wake patterns (unpublished data). If one role of melatonin is to stabilize the circadian system when other entraining factors (e.g. rest–activity and sleep–wake cycles) are disrupted (Illnerová et al., 1993), the combination of absent melatonin with abnormal entraining factors may have contributed to a vicious cycle that was expressed in the hypernychthemeral syndrome.

The fact that behavioral accommodation to a 24-hour rhythm in combination with timed light and dark exposure was able to induce a normal pattern of melatonin secretion suggests that the underlying mechanism for normal circadian melatonin production was always present in the patient. It appears that the melatonin regulatory system of the patient somehow responded to his highly unusual light exposure schedule with markedly reduced amplitude, possibly because it was periodically being flooded with light at unusual circadian phases. In this regard, it should be noted that another subject with an apparent hypernycthemeral syndrome was reported to have normal amplitude melatonin secretion (Hoban et al., 1989). In the case of our patient, it may be relevant that in some animals, brief light exposure at certain times is capable of suppressing melatonin production for the entire night (Reiter et al., 1986). This phenomenon has not been found in normal humans (Lewy et al., 1980).

It is unclear why the patient had no detectable serum melatonin while he was hypernychthemeral, yet had low detectable levels of urinary 6-sulfatoxymelatonin, the melatonin metabolite. An occult sympathetic degenerative disease might account for these data. Most probably, he produced minute amounts of melatonin or a variant of melatonin that was not detected by the serum assay but was eventually conjugated to form urinary 6-sulfatoxymelatonin, or the urinary 6-sulfatoxymelatonin that was detected was derived from the normally minor extra-pineal sources of serum melatonin such as the retina, the choroid plexus, or the gastrointestinal tract and the plasma melatonin from these sources was metabolized too quickly to be detected in the serum.

Monitoring the patient's light exposure clearly showed that he exposed himself to unusually low levels of light during the course of his day. If so, restoration of a distinctly

bright daytime versus night-time signal to the patient may have induced a normal pattern of melatonin secretion as well as behavioral entrainment to a 24-hour rhythm, although we can not exclude the possibility that this hormonal change resulted solely from enforcement of a 24-hour sleep–wake schedule. Though a recent report of the syndrome has suggested that hypernychthemeral syndrome may result from inappropriate photic exposure (Emens et al., 1994), we have no data to assess whether inappropriate photic exposure or the sleep schedule was the specific initial cause of this patient's syndrome.

A number of organic explanations of the patient's syndrome might be invoked. The behavioral capacity of the system to entrain following the treatment condition, however, attests to some degree of intact sensitivity to external light–dark cycles. The pineal gland was small and calcified on CT scan, but it is difficult to know whether these features were causes or results of the pineal gland's failure to secrete melatonin (or neither). The distinct performance and endocrine abnormalities were found in the gonadal and melatonin hormonal systems, which are directly regulated by the hypothalamus, and suggest a possible hypothalamic defect, perhaps in the circadian pacemaker cells of the suprachiasmatic nucleus or its retinal input. Whether such a postulated defect might have caused the patient's sleep–wake disorder, or whether it resulted from his environmental cave-like conditions, or both, is unknown. One could also argue that the circadian rhythm disorder is coincidentally associated in this patient with unrelated endocrine disturbances such as subclinical primary hypothyroidism and central hypogonadism.

Finally, the subtle change in the patient's sleep architecture after treatment merits comment. It is unclear whether the decline in delta (Stage 3 + Stage 4) sleep percentage from 15% to 8% and the rise in REM sleep from 20% to 28% is mechanistically a cause or effect of his improvement or merely an irrelevant artifact. Nevertheless, the association of his proportionate increase in REM sleep with his increased ability to awaken each morning is consistent with the 'sentinel' hypothesis of dream and REM sleep suggesting that a function of REM sleep is to facilitate awakening (Rivers, 1923; Snyder, 1966).

This case report highlights two matters that may be relevant to the diagnosis and treatment of other patients. Although the patient presented to us initially as having a pure sleep–wake disorder, we found significant co-existent endocrine abnormalities. The differential diagnosis of endocrine abnormalities should therefore include circadian rhythm disorders, so as to include therapeutic options outside of the realm of traditional drug and hormone-oriented endocrinology. Secondly, monitoring of ambient light exposure proved to be a simple and valuable tool in documenting the patient's pattern of exposure to light and in documenting compliance with the light treatment protocol. Light monitoring might therefore prove a useful diagnostic and treatment tool in other patients with circadian rhythm disorders.

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