Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome

In a study published in this Journal in 1992 Alvarez et al described normal profiles of plasma melatonin in a group of 12 patients with the delayed sleep phase syndrome, an idiopathic sleep disorder manifested by an inability to fall asleep and wake spontaneously at desired clock times and a phase delay of the major sleep cycle in relation to the desired time for sleep. Because of animal data indicating a central role of melatonin in circadian regulation, they obtained 24 hour plasma melatonin profiles of patients with delayed sleep phase syndrome in a fixed light-darkward environment (dark period 2300–0800). On average, plasma melatonin concentrations peaked about 0400 and reflected a normal adult pattern of melatonin secretion. Intrinsic patterns of human melatonin secretion, however, may be masked by patterns of sleep and light exposure. Evaluation of circadian oscillator rhythms are best unmasked in “constant routine” periods of at least 24 hours of virtual darkness that are designed to minimise or distribute evenly the possible “masking effects” of sleep, posture, exercise, meals, and light, which might distort the intrinsic patterns of circadian rhythms. Therefore, we evaluated circadian plasma melatonin concentrations and core body temperature with a 24 hour dark (<1 lux) period during routine waking in a patient with the delayed sleep phase syndrome.

A 43 year old woman presented to our clinic with a 30 year history of the delayed sleep phase syndrome, primarily manifested by an inability to fall asleep before 0400 and a difficulty in waking before 1200 daily. Although brain MRI when she was 36 had shown a pineal cyst, no other relevant abnormalities were discovered on routine physical examination or laboratory testing. Medical history included the removal of a right adnexa only for chronic cysts having undergone a complete hysterectomy at the age of 41 after complications from uterine fibroidectomY. There was no history of affective or psychotic disorders.

Over a six week period the patient unit the patient was tapered off benzodiazepines over four weeks and then remained medication free for another two weeks. She showed occasional irritability that was attributed to benzodiazepine withdrawal. During this period the patient was allowed to regulate her circadian exposure to light and dark and to sleep when she wished. Although she fell asleep was irregular from night to night, she would go to sleep between 0400 and 0830 each morning and sleep until 1000 to 1300. At the conclusion of this interval, a 24 hour constant routine procedure was undertaken whereby the patient was awake, in virtual darkness (<1 lux), and ate small isocaloric meals every two hours. She was kept awake by engaging her in conversation and sedentary games. Blood samples were obtained via an indwelling intravenous catheter every 30 minutes (1700–1700).

Plasma melatonin was measured by StockGrand Ltd (Department of Biochemistry, University of Surrey, UK) with a radioimmunoassay. Rectal temperature was monitored continuously throughout the procedure.

The patient’s plasma melatonin rhythm (figure), peaking at 0830, was remarkable particularly for its delayed phase position compared with that typically seen in normal subjects, which peaks in the middle of the night. Rectal temperature exhibited a similarly delayed profile with the nocturnal temperature minimum occurring between about 0500 and 1230.

The delayed timing of the plasma melatonin peak and the rectal temperature minimum provide preliminary evidence that a biological abnormality may be present in the delayed sleep phase syndrome and that the biological dysregulation matches the clinical features of the syndrome. Although it is theoretically possible that our plasma melatonin results differed from those of Alvarez et al because their sample consisted mostly of men and our patient was a woman, we have no reason to think that the sex difference might have accounted for the different melatonin profiles. Rather, we suspect that we were able to identify a phase shift in the melatonin profile because its underlying rhythm was unmasked by the 24 hour dim light conditions. Our finding of a similar delay in the circadian temperature rhythm confirms a previous report by Guilleminault et al. It is noteworthy that phase advancement of the circadian rhythm of body temperature has been associated with successful treatment of the delayed sleep phase syndrome.

If this report of delayed plasma melatonin and body temperature rhythms in the delayed sleep phase syndrome is replicated in a large sample of patients, it will provide further evidence that plasma melatonin and body temperature rhythms can serve as reliable markers of phase setting of the human body clock that regulates sleep. The establishment of a biological abnormality in this disorder might also provide some solace to those with the disorder, who until now, might have been told that their sleep disorder was psychogenic in origin. It will also provide biological markers for the diagnosis and progress of treatment of the syndrome.

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this unusual presentation of multiple system atrophy.

Patient 1 was a man who initially developed a sleep disorder at the age of 57. During sleep, he began to talk or even shout in arousals, recorded muscle jerks such as flinging his arms or lifting himself off the pillow. On several occasions he abruptly got out of bed and injured himself by colliding with furniture. His spouse had sustained several injuries in the morning, one apparent attempt at strangulation. These violent attacks lasted for a few minutes and occurred between midnight and 3:00 am. They could be aborted by forceful wakening. A few years later, the patient progressively developed a full picture of multiple system atrophy of striatogniral degeneration type with predominantly right sided akinetic rigid syndrome, unresponsive to levodopa, and subsequent impairment of postural reflexes, pyramidal signs, dysarthria and hoarseness, dysphagia, urinary incontinence and retention, impotence, postural hypotension with syncope, and autonomic dysregulation.

The violent behavioural episodes improved, but the nocturnal speech production persisted and snoring and episodes of stridor appeared. Electromyography showed denervation of the thyroarytenoid muscles and sphincter typically found in multiple system atrophy. Polysonomography with video showed stage 1 and 2 sleep with little deep non-REM sleep and a small proportion of REM sleep. During light sleep, there were episodes of bilateral fragmentary myoclonic twitches of arms, hands, and thumbs followed by widespread alpha activity for about 30 seconds. During REM sleep, there was atonia in central and segmental EMG apart from one episode of a sudden flinging movement of both arms with a related increase in EMG activity. No epileptic features were recorded during the episode. None of the other nocturnal behaviours described at the beginning of the disease were recorded on this occasion. There were no apnoeic episodes and no dips in oxygen saturation.

Patient 2 was a man who developed restless and disrupted sleep at the age of 42. He often shouted intelligibly, and sometimes lectured or reprimanded people. The patient was aware of this and said that it was not amusing. Periodically, he would jump out of bed, shake or groan in a stereotyped fashion, or flail his arms. Once he awoke out of bed in a rugby tackle, believing he was actually tackling someone. Such episodes occurred at around 5:00 am rather than soon after going to bed, from once a fortnight to twice a week. Episodes of snoring were also noticed. Two to three years later he progressively developed impaired coordination, slurred speech, impotence, and intermittent postural faintness. A full picture of multiple system atrophy of the olivopontocerebellar atrophy type was developed with prominent cerebellar, pyramidal, and dysautonomic signs and symptoms, and mild parkinsonian features. His nights were then predominantly affected by several episodes of stridor. At that time, five years after the onset of nocturnal problems, a sleep study recorded a normal sleep architecture with no excessive movements. No epileptic features or apnoeic periods were recorded, but the patient made "squeaking" noises on inspiration. The baseline saturation was 93% with minor dips throughout the study. Urethral sphincter EMG was again abnormal, and brain MRI showed moderate cerebellar atrophy.

The two patients described developed clinically probable multiple system atrophy of stratonigral degeneration type (case 1) and olivopontocerebellar atrophy (case 2) types. In both cases, pronounced sleep disturbances were the first recorded complaint, preceding the onset of the first motor or autonomic symptoms by two to three years. Such sleep disorders, with a history of violent and potentially harmful behaviour and reported vivid dream mentation appropriate to the observed action, are typical of REM sleep behaviour disorder sleep behavior. Sleep evaluations were subsequently documented by the recording of a less severe episode in patient 1 during a sleep telemetry study.

Chronic REM sleep behaviour disorder is often reported to be idiopathic and can coincidentally have appeared in these two cases. Beyond the temporal association, however, there are other reasons to believe that REM sleep behaviour disorder was the first manifestation of multiple system atrophy in these patients. Thus REM sleep behaviour disorder has also previously been described during the course of, 1 or before the onset of, multiple system atrophy and in familial olivopontocerebellar atrophy, the pathology of which bears some similarity to that of multiple system atrophy. It has also been described in idiopathic Parkinson's disease, occurring late in the disease, but occasionally preceding other symptoms. 3 REM sleep behaviour disorder is thought to originate from a dysfunction in pontine structures generating REM sleep muscle atonia. 1 4 5 6 7 8 9 10 The loss of, or disappearance of, REM sleep muscle atonia has been documented after experimental pontine lesions, 9 and pontine lesions are almost always found in both striatogniral degeneration and olivopontocerebellar atrophy variants of multiple system atrophy, with a more restricted involvement of the locus ceruleus in idiopathic Parkinson's disease. 10 It is therefore likely that REM sleep behaviour disorder is the first manifestation of pontine involvement due to multiple system atrophy in our two patients, and has to be added to the growing list of unusual clinical presentations of multiple system atrophy that should be clinician aware. 11 12 These two cases also underline the fact that REM sleep behaviour disorder is not always idiopathic, but can instead herald the onset of a major neurodegenerative disorder. 11 12