LETTERS TO THE EDITOR

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-wake cycle in relation to the desired time for sleep.1 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-dark 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.2 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.3 Therefore, we evaluated circadian plasma melatonin concentrations and core body temperature with a 24 hour dark (<1 lux) period in a constant routine 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 manifest 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. Menstrual history showed only four menstruations 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 inpatient 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 slept 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.4 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.5

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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The "squeaking" periods impaired his ability to fall asleep and the patient would frequently 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. The attacks progressed over a few years, the patient developing a full picture of multiple system atrophy of striatogniral degeneration type with predominantly right sided akinetic rigid syndrome, unresponsive to levodopa. The most noticeable feature was the absence of postural reflexes, pyramidal signs, dysarthria and hoarseness, dysphagia, urinary incontinence and impotence, postural hypotension with syncope, and autonomic dysfunction. The violent behavioural episodes improved, but the nocturnal speech production persisted and snoring and episodes of stridor appeared. Electromyography showed denervation of the genioglossus muscle and sphincter EMG was again abnormal, and brain MRI showed moderate cerebellar atrophy. The two patients described developed clinically probable multiple system atrophy of striatogninal 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 symptom by one 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. 1-3 The sleep behaviour disorder was 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 associated with olivopontocerebellar atrophy and could 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, or before the onset of, multiple system atrophy 4 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, 5 but the disease, but occasionally preceding other symptoms. 6 REM sleep behaviour disorder is thought to originate from a dysfunction in pontine structures generating REM sleep muscle atonia. 7 Atopy and disappearance of REM sleep muscle atonia have been documented after experimental pontine lesions, 8 and pontine lesions are almost always found in both striatogninal degeneration and olivopontocerebellar atrophy variants of multiple system atrophy, with a more restricted involvement of the locus ceruleus in idiopathic Parkinson's disease. 9 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 recognised. 10 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

Crying seizures after cerebral infarction

Ictal crying is a relatively rare epileptic condition. 1 There have been 11 such cases reported before 1993. Recently seven more cases were reported by us in children. 2 The aetiology of the crying seizures in these patients was attributed to tumour, vascular malformations, or mesial temporal sclerosis. There have been no previous case reports of ictal crying after cerebral infarction. We report a case of crying seizures in a patient after cerebral infarction with a seizure focus in the right temporal region.

The patient was a 66 year old right handed man developed dizziness and a left hemiparesis that resolved over a five day period. He was placed on aspirin (325 mg three times daily). The patient did well until two years later when he awoke with a left hemiparesis. There was no sensory loss or ataxia. Carotid doppler imaging, trans-thoracic echocardiography, and cardiac monitoring were unremarkable. Brain MRI showed multiple focal ischaemic changes in the white matter, most notably in the posterior limb of the right internal capsule, and mild diffuse cerebellar atrophy. The patient was treated on ticlopidine (250 mg twice daily).

The patient did well until seven months later when he began exhibiting unusual behaviour including inappropriate speech and episodes in which he would suddenly stop talking and stare, and episodes of eye deviation to the left. On admission to hospital he was seen to exhibit repeated episodes of deviation of the head and eyes to the left during which time he would begin crying. During these crying episodes he remained alert, answered questions appropriately, and denied any subjective experience of sadness or depression. Electroencephalography performed during these episodes showed ictal discharges occurring repeatedly over the
REM sleep behaviour disorder as the presenting symptom of multiple system atrophy.

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