Clinical Case Report

Parkinsonian syndromes presenting with circadian rhythm sleep disorder–advanced sleep-phase type

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ABSTRACT

Background. Circadian rhythm sleep disorder–advanced sleep-phase type is a relatively uncommon disorder, mostly seen among the elderly population. Impaired circadian rhythms have been reported in neurodegenerative conditions; however, there are no reports of any circadian rhythm sleep disorder among patients with Parkinsonian syndromes. We report two patients who presented with this circadian rhythm disorder, and were then diagnosed with a Parkinsonian syndrome.

The cases. A 65-year-old retired man presented with history of abrupt change in sleep schedules, sleeping around 6.30–7 p.m. and waking up around 3–4 a.m. for the last 2 months. On detailed examination, the patient was observed to have symmetrical bradykinesia and cogwheel rigidity of limbs. A diagnosis of multiple system atrophy was made, supported by MRI findings and evidence of autonomic dysfunction. Symptoms of change in sleep–wake cycles resolved over the next 1 year, while the patient was treated with dopaminergic therapy.

A 47-year-old man, who was being evaluated for pre-surgical investigation for refractory temporal lobe epilepsy, presented with complaints suggestive of dysarthria, bradykinesia of limbs and frequent falls for 5 months. Simultaneously, he began to sleep around 7 p.m. and wake up at about 2–3 a.m. Examination revealed severe axial rigidity, restricted vertical gaze and bradykinesia of limbs. A diagnosis of progressive supranuclear palsy was made.

Conclusion. This is the first report of Parkinson's plus syndromes presenting with a circadian rhythm sleep disorder–advanced sleep-phase type. More prospective assessment for circadian sleep disorders may introduce useful insights into similar associations.

Natl Med J India 2015;28:233–5

INTRODUCTION

Circadian rhythms are self-sustaining rhythms regulated at a molecular level and persist in the absence of external time cues with a periodicity of approximately 24 hours. The sleep–wake cycle is one of the most important and apparent circadian rhythms in humans. The circadian rhythm sleep disorder (CRSD)–delayed sleep-phase type is the commonest endogenous CRSD and typically presents during adolescence or early adulthood. CRSD–advanced sleep phase (CRSD–ASP) is less common and typically presents among the elderly.[1] Ageing is known to be associated with less robust circadian rhythms, decrease in endogenous melatonin secretion and advance of the circadian sleep cycle.[2] Impaired circadian rhythms are associated with many neurodegenerative disorders.[3] However, there are no published reports on the co-occurrence or association of any of the CRSDs with Parkinson's disease or Parkinson's plus syndromes.

We report two patients who presented with CRSD–ASP and on detailed evaluation were found to be suffering from a Parkinsonian syndrome.

THE CASES

Case 1

A 65-year-old retired man presented with a history of excessive sleepiness for 5 months. He would fall asleep around 7 p.m. in the evening and had to be forcibly woken up for a few minutes for dinner. He would wake up at 4 a.m. and feel fresh on awakening. In the pre-morbid state, he used to go to bed around midnight and wake up at 7 a.m. feeling refreshed. He did not report any snoring, excessive sleepiness or fatigue during the daytime. A history of occasional dream enacting behaviour for the past 5 months was present (Fig. 1).

On the initial examination, the patient appeared hypomimic; on being directly questioned regarding motor activities, he came up with the complaint of slowness of activities, taking almost twice the usual time to finish his meals, bathe and dress. He also had a history of urgency and precipitancy of micturition and recent onset erectile dysfunction. There was no history to suggest tremor, gait disturbance, postural hypotension, diarrhoea, constipation, or decreased or increased sweating. He had diabetes and hypertension, and a minor stroke 7 years ago. There was no history of any drug addiction or substance abuse.

The patient was an elderly man of pleasant disposition and average built and nutrition.There was a significant drop in blood pressure from 150/90 mmHg in the supine position to 120/80 mmHg three minutes after standing. No cognitive deficit was identified. Mildly slowed ocular pursuits were observed. Motor examination revealed symmetric cogwheel rigidity and brady-kinesia. There were no cerebellar signs. Detailed autonomic function testing revealed poor autonomic tone with loss of reactivity. An ultrasound revealed no enlargement of the prostrate and the bladder did not show any evidence of cystitis. The residual urinary volume was 55 ml. MRI of the brain was normal. A diagnosis of multisystem atrophy was considered. Dopaminergic therapy was started. His sleep–wake rhythm normalized over 6 months, and he reported about 50% benefit with levodopa–carbidopa. He progressed rapidly and became severely bradykinetic over the next 18 months, even on increased dosage of the levodopa–carbidopa combination (maximum 625 mg per day). The presence of relatively rapidly progressive, symmetrical Parkinsonism with severe autonomic dysfunction, with only partial and ill-sustained response to dopaminergic therapy, a diagnosis of multiple system atrophy (MSA) progressive was probable. The patient died 2 years later.

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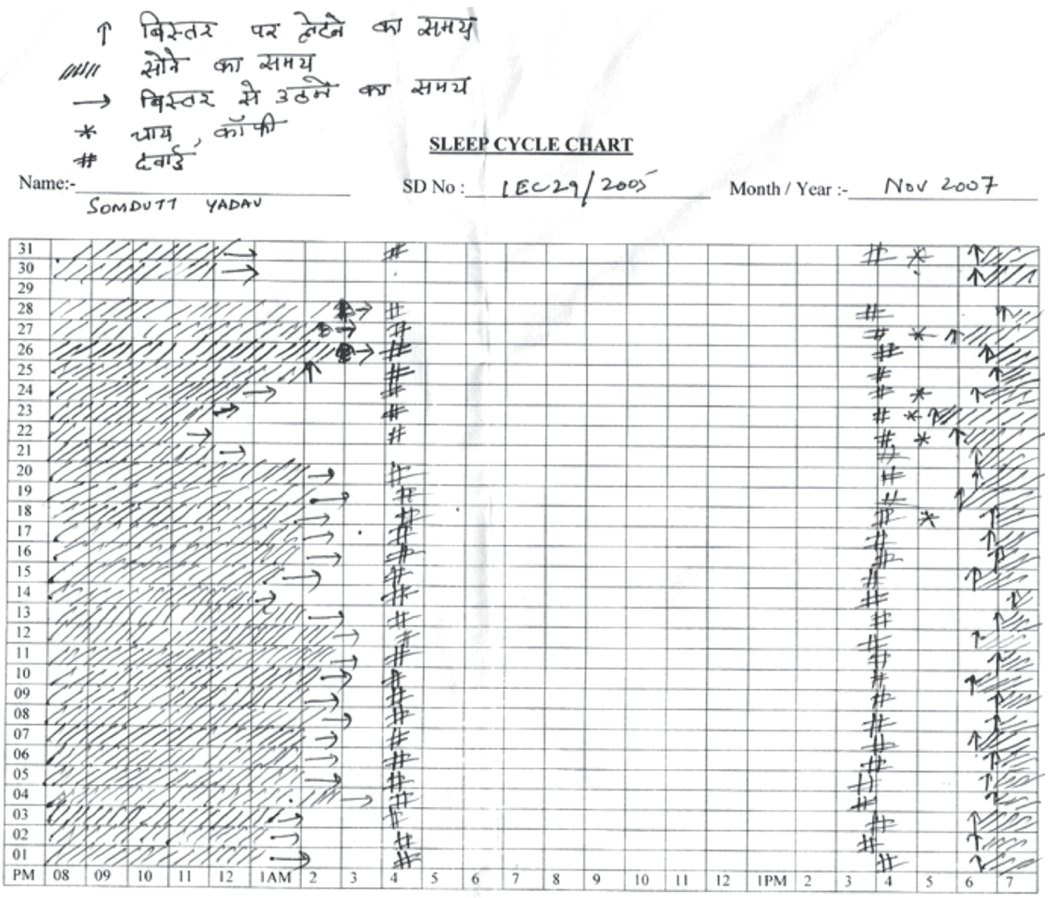

FIG 1. Sleep log of case 1

Case 2

A 47-year-old man, who was undergoing pre-surgical investigation for refractory temporal lobe epilepsy for 3 years, presented with complaints of recent-onset unprovoked falls and progressive reduction in clarity of speech for the past 8–9 months. On an outpatient basis, a possibility of anti-epileptic induced cerebellar toxicity was considered. However, there was another prominent symptom, that of sleeping too early in the evenings and waking up between midnight and 2 a.m., hence a detailed re-assessment was done and it was found that the falls were backwards, and not associated with loss of consciousness or unresponsiveness. He also gave a history of marked slowing in all activities of daily living for the past 5 months, taking 2–3 times longer to complete his daily activities such as brushing, bathing and dressing. His family had noticed a change in his gait, with short quick steps. These symptoms were noticed on both sides simultaneously. The volume of his speech had become lower and the words were unclear. There was no history of tremor or any abnormal posturing of limbs. The family members denied any history to suggest cognitive decline. He had no urinary complaints or erectile dysfunction. Simultaneously, he began to sleep around 7 p.m. and wake up at 2–3 a.m. He had to be woken up for dinner. No other sleep-related complaints were obtained. Examination revealed a dystonic facies with a staring look and infrequent blinking. Higher mental function testing revealed frontal subcortical impairment. Volitional extraocular movements were grossly restricted both in the vertical and horizontal directions, with preserved vestibule-ocular reflex. He had severe axial rigidity and bradykinesia of limb movements. A clinical diagnosis of progressive supranuclear palsy was made.

MRI of the brain revealed midbrain atrophy. The patient was started on the levodopa–carbidopa combination to which he did not show any significant response. His falls worsened and he gradually became bed-bound. His sleep pattern normalized spontaneously over the next 10–12 months. The patient died 3 years later at home with severe swallowing disability.

DISCUSSION

We describe two similar patients, in whom CRSD–ASP type was one of the presenting manifestations of a Parkinsonian plus syndrome. This association has not been previously described. We discuss the pathophysiological basis of this, as hypothesized by us, based on evidence from literature published on animal models as well as humans with either of these syndromes.

In an elegant experiment on *Drosophila melanogaster* mutants which display clock-unrelated neurodegenerative phenotypes, Krishnan *et al*. combined a null mutation in the clock gene period (per01) which abolishes circadian rhythms, with a hypomorphic mutation in the carbonyl reductase gene sniffer (sni1), which displays oxidative stress-induced neurodegeneration.[4] The investigators observed that disruption of circadian rhythms in sni1 mutants significantly reduces their lifespan compared to single mutants; that the shortened lifespan in double mutants was coupled with accelerated neuronal degeneration evidenced by vacuolization in the adult brain and that, in addition, per01 sni1 flies showed drastically impaired vertical mobility and increased

accumulation of carbonylated proteins compared to age-matched single mutant flies. They concluded that the period gene may be causally involved in neuroprotective pathways in ageing drosophila.

Sleep disturbances are a well-characterized feature of the non-motor symptom complex of Parkinson's disease (PD). The causes of sleep disturbance are multifactorial, but pathological degeneration of central sleep regulation centres in the brainstem and thalamocortical pathways is a key mechanism. The sleep disturbances range from insomnia through excessive daytime sleepiness and importantly, rapid eye movement (REM) behaviour disorder, which has been established as a precursor of synucleopathies such as PD, dementia with Lewy bodies and multisystem atrophy.[5] CRSD, however, has so far not been described as a feature of either PD or Parkinson's plus syndromes. In a recent review, Videnovic *et al.* quote several studies pointing towards clear circadian variations in the various manifestations of PD, mainly motor, visual, autonomic and drug effects.[6] The authors mention that the impact of circadian dysregulation of sleep in PD populations has not been systematically assessed yet.[6] Advanced sleep phase syndrome (ASPS) was the presenting feature in the first patient and a prominent clinical feature in the second patient, described here, both of whom subsequently went on to develop atypical Parkinsonian syndromes.

ASPS and multisystem atrophy

There is no report in the existing literature about CRSD in MSA. However, alteration of other circadian rhythms, also controlled by the hypothalamus has been described. Ozawa *et al.* reported the depletion of arginine vasopressin neurons in the suprachiasmatic nucleus of the hypothalamus in a single case of MSA with concomitant preservation of magnocellular arginine vasopressin (AVP) neurons.[7] The authors hypothesized that impaired circadian regulation of endocrine and autonomic function in MSA could be attributed to loss of AVP neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus. Abnormal circadian fluctuations of plasma (AVP)[7] and cortisol,[8] as well as impaired physiological nocturnal fall in body temperature[9] have been reported in MSA. An autopsy series of 5 MSA patients found a consistent loss of AVP neurons in the SCN of the hypothalamus.[10] In a study comparing the circadian pattern of gastric myoelectrical activity in 14 MSA patients with 9 healthy controls, Suzuki *et al.* found that normal subjects have a circadian pattern in the dominant frequency of their electrogastrograms, which is significantly blunted among patients with MSA.[11] These observations suggest that the presentation with ASPS in the above patient of multisystem atrophy may, in fact, have been an unusual or perhaps an under-reported manifestation of the neurodegenerative disease process itself in which the normal circadian rhythms controlled by the SCN are altered.

ASPS and progressive supranuclear palsy

There are no reports in the existing literature on the presence of ASPS in patients of PSP. However, there has been interest in studying sleep-related issues in patients with this Parkinsonian syndrome. Several years ago, Montplaisir *et al*. reported clinical and polysomnographic features of sleep among 6 patients with PSP and compared the same with a similar number of normal controls.[12] No information, however, is available from this paper on circadian sleep rhythms among this population.[12]

Conclusion

This is the first report of Parkinson's plus syndromes presenting with CRSD–ASP. While REM sleep behaviour disorder is now well established to be a harbinger of these neurodegenerative disorders, more prospective assessment for circadian sleep disorders may introduce useful insights into similar associations.

Conflict of interest: None

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