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Case report

Development of restless legs syndrome after dopaminergic treatment in a patient with periodic leg movements in sleep

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Abstract

Periodic leg movements in sleep (PLMS) unrelated to restless legs syndrome (RLS) are a polysomnographic finding with a controversial clinical value. We describe a patient with isolated periodic leg movements in sleep (without any awake or sleep complaints), who developed severe diurnal RLS symptoms a few months after starting dopaminergic treatment, a phenomenon mimicking augmentation. The diurnal RLS symptoms disappeared after withdrawal of the dopaminergic drugs. Serum ferritin levels were relatively low (31–61 mcg/l; normal: 30–400 mcg/l). Since low levels of ferritin have been implicated in the genesis of RLS, and augmentation is a phenomenon associated with RLS, our findings here suggest that asymptomatic PLMS may have pathogenic mechanisms similar to RLS. Isolated PLMS and RLS could be, at least in some cases, different clinical forms of the same disorder. The conjunction of dopaminergic treatment with low ferritin levels may expose a patient with isolated PLMS to the development of RLS. Discontinuation of dopaminergic drugs in patients with isolated PLMS who develop RLS during the course of the treatment would be a reasonable recommendation.

Keywords: Restless legs syndrome; Restless legs augmentation; Periodic leg movements in sleep; L-dopa; Pergolide

1. Introduction

Periodic leg movements in sleep (PLMS) are a polysomnographic (PSG) finding characterized by the presence of periodic bursts of leg (or arm) electromyographic (EMG) activity during sleep associated with discrete, sterotyped movements of the legs or arms, usually during NREM sleep [1,2]. Such movements, although typically seen in patients with restless legs syndrome (RLS), do not occur in 12–20% of these patients [3] and are not specific to RLS because they also occur in other disorders [1], such as REM sleep behavior disorder or narcolepsy, among others. Outside the context of RLS, PLMS have a controversial clinical value: whereas for some authors they have no clinical meaning [1,4], others believe they might have some relevance if associated with insomnia or hypersomnolence, particularly with a frequency higher than that in an age-related control population and with associated arousals [5,6]. Both points of view agree, however, in that RLS and PLMS are different disorders. We report here a patient with asymptomatic PLMS who developed a typical RLS after starting dopaminergic treatment, resembling the augmentation phenomenon described in treated RLS patients [7].

2. Patient description

A 50-year-old man consulted because of his wife's complaints of his sleep-related movements, described by her as brisk flexions of the legs or legs and arms, usually involving the side of his body not lying on the bed, and occurring once or twice per minute throughout the night. They awakened her repeatedly, especially at the beginning and at the end of the night, but did not disturb the patient. The movements were first noticed after they married, when the patient was 28 years old, and worsened steadily throughout the next 14 years. When he was 42 years old, after starting to work night shifts (22:00–06:00 h), the movements increased in frequency although the patient only complained of occasional difficulty in falling asleep after the night shift. Four years later and until the present he returned to a day shift, during which time he experienced no difficulty in falling sleep but progressive worsening of the leg movements during sleep, despite treatment for a few

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months with several benzodiazepines and sodium valproate. The patient's sister, who died several years before, probably had a similar problem.

General and neurological examination was normal with a mild increase in deep tendon reflexes and a brisk withdrawal response to nociceptive simuli in the plant of both feet. In response to specific questioning the patient repeatedly denied the presence of hypersomnia, any difficulties in initiating or maintaining sleep, or diurnal symptoms suggestive of RLS. The Epworth sleepiness scale score was 6. Results of blood tests, including iron levels, were normal, but ferritin was in the lower end of the normal reference values of the laboratory (31 mcg/l in 1998 and 61 mcg/l in 2001; normal values 30–400 mcg/l)). An EMG examination was normal. A nocturnal PSG (Table 1) showed a normal sleep architecture with very frequent PLMS (PLMS index of 102), particularly in NREM sleep and decreasing during the last hour of sleep. The majority (98%) of the movements were not associated with arousals or awakenings.

We treated the patient with slow release L-dopa (Sinemet® CR, levopoda 200 mg, carbidopa 50 mg), increasing slowly up to 300 mg of levodopa at bedtime, with a significant improvement in the movements followed 4 months later by their reappearance during the last third of the night. We added 100 mg of slow release L-dopa at 04:00 h, with no significant change in the movements. After 7 months of treatment the patient began to experience paresthesias in the perineal area and legs, accompanied by an unpleasant desire to move his legs, occurring at different times of the day but clearly worse in the evening. A repeated PSG (Table 1) disclosed a dramatic reduction of the movements (PLMS index of 13) during the first two thirds of the night but not the last third, and an increase in the percentage of stage III–IV sleep. L-dopa was withdrawn with disappearance of the diurnal RLS symptoms. Two weeks later we started pergolide 0.05 mg at bedtime, increasing slowly up to 0.25 mg, again with transient improvement of the PLMS during several weeks followed by later worsening. Further dose increases decreased the movements but at 0.40 mg, and especially at 0.60 mg/day, the patient developed daily, diurnal perineal and leg paresthesias, clearly worse with rest and in the afternoon and evening, accompanied by a strong desire to move his legs to relieve the symptoms. This resulted in sudden pushes to the brake or accelerator which forced him to stop driving. Pergolide was progressively withdrawn with disappearance of the RLS and recurrence of the PLMS.

Table 1
PSG findings before and 7 months after levodopa[a]

	Baseline	After 7 months of L-dopa
TST (min)	424	440
Sleep efficiency (%)	90	91
Stage I (%)	16.7	11.7
Stage II (%)	61.5	50.23
Stage III–IV (%)	6.6	21.14
Stage REM (%)	15.2	16.93
PLMS index	102.5	13
PLMS arousal index	2.2	2

[a] TST, total sleep time; sleep efficiency, total sleep time divided per total time in bed; PLMS index, number of periodic leg movements per hour of sleep; and PLMS arousal index, number of PLMS associated with arousal per hour of sleep.

3. Discussion

This patient had isolated PLMS in the absence of diurnal complaints suggestive of RLS, sleep fragmentation, hypersomnia or insomnia. After treatment with slow release L-dopa, and particularly with pergolide, he developed severe RLS symptoms [8] which disappeared after withdrawal of the dopaminergic drugs. This clinical presentation is not suggestive of drug withdrawal (the RLS symptoms extended to a time of day not compatible with it) and mimicks the augmentation phenomenon described in RLS patients [7]. Augmentation is characterized by a relative worsening of RLS symptoms – either in intensity, duration or body parts involved – which continues until the dopaminergic treatment is decreased or withdrawn [2,7]. Augmentation does not appear in other movement disorders and has only been described in patients with RLS and symptomatic PLMS (that is, PLMS patients with associated clinical sleep disruption or daytime somnolence), although augmentation in RLS is much more common than in PLMS (82 versus 31%, respectively with levodopa; 17 versus 0% with pergolide) and more severe (50 versus 13% with levodopa) [7,9]. It is not, however, clear that these PLMS patients developed all the symptoms of RLS. In our patient we found, simultaneous with the development of the full RLS tetrad, a decrease in the PLMS index after dopaminergic treatment. It is not known whether or not the medication continues to reduce the PLMS in patients with RLS who develop augmentation, but it has been assumed that it does. Our finding is consistent with the clinical reports of augmentation which note continuing benefit (e.g. good sleep) with treatment, but worsening RLS symptoms during the day [9].

The exact mechanism by which augmentation occurs is unknown [2,7]. The importance of iron metabolism in RLS is underscored by reports of low levels of serum ferritin – as well as of brain iron, measured by magnetic resonance imaging [10] – in RLS patients, and correlation of RLS severity with serum and CSF ferritin levels [11]. Our patient had relatively low levels of ferritin which may have made him more sensitive to augmentation with dopaminergic treatment. The familial pattern may also suggest a relation to RLS [2].

Our findings suggest that it would be reasonable to recommend discontinuation of dopaminergic agents in

patients with PLMS who develop RLS during the course of the treatment and to consider alternative therapies for patient and bed partner. It should also be considered that in some cases the development of RLS after PLMS could simply be due to progression of the disease.

Overall, this case suggests that RLS and some cases of isolated PLMS probably share similar pathophysiologic mechanisms indicating that, at least in some patients, they could be two clinical presentations of the same disorder.

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