Effective treatment of Restless Legs Syndrome by Safinamide in Parkinson's Disease patients.

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BACKGROUND

Parkinson's Disease (PD) is often associated with insomnia, REM sleep behavior disorder, sleep-related breathing disorders and restless legs syndrome (RLS). Safinamide is a monoaminoxidase-B inhibitor (IMAO-B) approved as add-on therapy to levodopa (LD) in PD. Here, we report two cases of motor fluctuating PD patients, who experienced the improvement of RLS symptoms after starting Safinamide as add-on to LD.

CASE 1

A 60-year-old woman affected by PD with motor fluctuations (see Table), and treated by LD/Carbidopa (CD) 500/125 mg/day, complained of difficulty in falling asleep and frequent nocturnal arousals. She experienced an unpleasant sensation in the legs, which occurred when she was relaxed and/or during nighttime, again urging her to move her legs for several years before starting LD treatment. Polysomnography (PSG) showed nocturnal sleep impairment and frequent periodic limb movements (PLMS) (Table). The secondary causes of RLS were excluded and serum ferritin levels were in the normal range. The patient then started safinamide up to 100 mg/day for better controlling her motor PD symptoms. At three-month follow-up, she reported the improvement of PD symptoms associated with the remarkable reduction of RLS symptoms (Table). Consistently, the PSG showed the significant reduction of PLMS coupled with the reduction of sleep fragmentation (Table).

CASE 2

A 56-year-old PD patient, treated with LD/CD/Entacapone 500/125/1000 mg/day, presented to our outpatient clinic because of PD motor symptoms fluctuations (Table). He also reported symptoms indicative of RLS, since he experienced troublesome sensory-motor symptoms in the legs; these occurred when he was lying in bed and these symptoms urged him to walk to obtain relief. RLS symptoms appeared two years before motor fluctuations and were not time-related to LD therapy. After exclusion of secondary causes of RLS (also counting normal serum ferritin levels), the patient performed PSG documenting nocturnal sleep quality reduction and several PLMS (Table). For the treatment of motor symptoms, he was prescribed safinamide up to 100 mg/day. At three-month follow-up, he reported the improvement of PD symptoms and marked reduction of RLS symptoms (Table). PSG documented the striking reduction of PLMS coupled with the improvement of sleep quality (Table).

	Case 1		***Case 2***	
Clinical Data	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
H&Y	3	3	3	3
UPDRS-III	25	21	32	29
UPDRS-IV	3	0	5	2
IRLSS	28	5	23	6
PSG data	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
TST (min)	303.4	376.8	322.2	370.6
SE (%)	67.8	86.4	63.4	85.8
SL (min)	57.5	22.5	65.5	17.5
WASO (min)	144.1	59.3	186	61.3
PLMI	48.7	8.9	57.3	12.5
AHI3%	3.6	4.5	5.4	3.9

Abbreviations: H&Y, Hoehn and Yahr; MDS, Movement Disorders Society; UPDRS-III, Unified Parkinson's Disease Rating Scale-motor section; UPDRS-IV, Unified Parkinson's Disease Rating Scale-fluctuation section; IRLSS, International Restless Legs Syndrome Study Group rating scale; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; WASO, wakefulness after sleep onset; PLMI, periodic limb movements per hour; AHI, apnea-hypopnea index associated with 3% oxygen desaturation.

CONCLUSIONS

RLS is a sleep disorder with a clinical diagnosis based on the urge to move the legs associated with uncomfortable and unpleasant sensations that lead with poor sleep quality and continuity. The hypothetical etiology of RLS is multifactorial: altered brain iron transportation, dopaminergic dysfunction of mesolimbic and nigrostriatal pathways, and thalamic glutamatergic hyperactivation.

RLS in PD ranges from 0.5% to about 16.5%, and increases in prevalence during the course of disease, frequently occurring in moderate-advanced patients. Dopamine-agonists, α2δ ligands and opioids represent the current treatments for RLS. However, RLS treatment in PD is not always straightforward, since therapeutic strategies may be limited by co-morbidity and severity of disease.

In this report, we diagnosed RLS in two patients co-affected by PD. RLS in PD patients could be in differential diagnosis with LD-induced dyskinesia, which usually have a direct temporal relationship with LD therapy. Our patients did not show LD induced dyskinesia and did not report nocturnal OFF periods, but presented the clinical diagnostic criteria of RLS, coupled with PSG documenting PLMS. This report showed that safinamide 100 mg/day added to LD, prescribed according to common clinical practice and indication in motor fluctuating PD patients, other than improving patients' motor symptoms, was useful to ameliorate RLS and reduce PLMS. Therefore, we hypothesize that safinamide, in addition to its dopaminergic activity as selective IMAO-B, may act on RLS also through its non-dopaminergic action, reducing the glutamatergic hyper-activation. Consistently, since this is a clinical experience, we cannot exclude a possible placebo effect of safinamide on RLS symptoms; further studies with larger samples of PD patients are needed to endorse the present observation.