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Restless legs syndrome (RLS), Parkinson's disease, and sustained dopaminergic therapy for RLS

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1. Introduction

The Swedish neurologist and surgeon Karl A. Ekbom described restless legs syndrome (RLS; see Table 1 for diagnostic criteria) in 1945 – therefore, RLS is often known as Ekboms's disease [1]. However, the English physician Sir Thomas Willis may have described RLS as early as 1672 [2]. RLS is a movement disorder that is distinct from periodic limb movements during sleep (PLMS), which are abnormal, involuntary movements that occur mainly during sleep but occasionally during relaxed wakefulness. PLMS may accompany RLS, but PLMS occurs more commonly without RLS [3,4]. Diagnosis of PLMS usually requires polysomnography, whereas RLS remains a clinical diagnosis by definition [5]. RLS can be effectively treated by almost any medication that also treats Parkinson's disease (PD). In this two-part paper we present new information on the clinical overlap of RLS and PD (Section 2) and review the use of sustained dopaminergic treatment as it applies to RLS (Section 3).

2. Clinical overlap of RLS and PD

2.1. Pathophysiology and clinical associations compared to PD

The underlying cause for RLS and PLMS is unknown, but involvement of the central and peripheral nervous systems due to vascular, genetic, iatrogenic, and metabolic components have been proposed. The central dopaminergic systems, particularly the nigrostriatal system and the mesocorticolimbic system, have been implicated in the pathophysiology of RLS. This hypothesis is supported by the beneficial effects of various dopaminergic agents in the treatment of RLS [6]. However, brain imaging studies have reported conflicting data. In a study utilizing ^{123}I-IBZM SPECT, Eisensehr et al. found no differences in dopamine transporter binding or type-2 dopamine receptor (D2) binding between RLS patients (drug naïve or levodopa-treated) and healthy controls [7,8]. However, other studies have shown reduced striatal D2 receptor binding using ^{123}I-IBZM and [^{11}C]raclopride, suggesting dopaminergic dysfunction in RLS patients [9,10]. Three [^{18}F]dopa PET studies have been reported and two have shown a slight but significant decrease in striatal [^{18}F]dopa uptake in PLM-RLS patients compared to healthy controls, suggesting a presynaptic dopaminergic dysfunction in the striatum [11,12]. However, an intermittent decrease in dopamine turnover with relatively normal intrasynaptic dopamine levels; dysfunction of alternative dopamine-dependent pathways such as the diencephalospinal pathway; or neuropeptide-related (e.g. orexin) neuronal dysfunction cannot be excluded as factors underlying the symptoms of RLS [6,13]. PLMS may also have a dopaminergic basis and it has been suggested that PLMS arises from a loss of supraspinal inhibitory impulses resulting in enhanced facilitation of spinal flexor reflexes. Spinal flexor reflexes appear to be under partial dopaminergic control [14].

2.2. Co-morbidity of Parkinson's disease and restless legs syndrome

Few studies have systematically addressed the issue of RLS occurring co-morbidly with PD. This issue is compounded by the fact that RLS is often treated with dopaminergic drugs, and symptoms of RLS may overlap with other symptoms such as akathisia and nocturnal motor fluc-

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Table 1
Criteria for diagnosis of idiopathic RLS[a]

Minimum diagnostic criteria	Additional features
● Desire to move limbs, usually associated with paresthesia/dysesthesia	● Sleep disturbance
● Motor restlessness	● Periodic limb movements in sleep
● Symptoms worse or exclusively present at rest – partial/temporary relief with activity	● Neurological examination normal
● Symptoms worse in the evening or at night	● Chronic symptoms with exacerbations and remissions
	● Positive family history

[a] Data from International Restless Legs Syndrome Study Group [7]. Note that response to dopaminergic agents, although often present, is not regarded as a criterion for diagnosis of idiopathic RLS.

tuations. A study by Ondo et al. analyzed the records of 303 PD patients and found that 19.5% of these patients also had RLS [15]. Ongoing studies in our unit suggest a similar rate of RLS symptoms in PD patients of approximately 20% (unpublished observations). Arnulf et al. have suggested that routine polysomnography and multiple sleep latency test (MSLT) evaluation in PD would unmask PLMS in 15% of cases [16]. An increased PLMS index has also been reported in untreated PD patients [17].

Evidence accumulating from the natural history of levodopa-treated RLS also suggests similarities with PD. The phenomena of rebound and augmentation usually seen after chronic levodopa treatment of RLS is phenomenologically similar to fluctuations in motor responses and dyskinesias that occur in PD patients after long-term levodopa treatment. Most PD patients have poor and fragmented sleep due to a range of motor, sensory, urinary, and neuropsychiatric problems [18], including RLS or symptoms resembling RLS [19]. Therefore, it is possible that a reduction in central dopaminergic transmission in PD and/or ongoing dopaminergic therapy of PD predisposes patients to a syndrome of nocturnal restlessness resembling symptoms of RLS and PLMS without the presence of clinically-defined RLS.

2.3. Methods

Using the newly-developed Parkinson's Disease Sleep Scale (PDSS) – a PD-related, 15-item visual analogue scale now being used in the United Kingdom, Germany, Spain, and Japan [19] – we have recently evaluated the issue of nocturnal restlessness and its impact on daytime sleepiness in PD [20]. The scale evaluates 15 commonly-reported symptoms associated with sleep disruption in PD. Items 4, 5, 10, and 11 of the scale address nocturnal restlessness or associated features, while other items focus on insomnia, excessive daytime sleepiness (EDS), nocturnal akinesia, nocturia, and neuropsychiatric phenomena [19]. Clinical records of 156 consecutive PD patients (97 male, 59 female) who had completed the PDSS while attending outpatient clinics were analyzed. The mean age of the patients was 67.0 ± 9.7 years, mean duration of disease was 5.8 ± 5.1 years, and the mean Hohen and Yahr scale score was 2.7 ± 0.7 years. The patients completed the scales with additional corroboration from their caregivers.

In order to investigate the impact of RLS-type symptoms (we termed this nocturnal restlessness) on daytime functioning, total scores for nocturnal restlessness were correlated with specific items of the PDSS relating to overall quality of night's sleep, sleep onset, sleep refreshment, and propensity to unexpectedly fall asleep during the day. Scores were also correlated with demographic measures of age, disease duration, and disease severity (Hoehn and Yahr stage).

2.4. Results

Subjects included 130 patients on dopaminergic treatment (none were receiving neuroleptics) and 26 untreated patients ranging from early to advanced disease. In addition, 46 non-parkinsonian healthy adults also completed the PDSS (16 male, 30 female; mean age 54.2 ± 12.5 years).

The mean total score for the four items of the PDSS relating to nocturnal restlessness was 27.5 ± 8.1 in PD patients, which was significantly lower ($P < 0.01$) than the scores of non-parkinsonian, healthy adult controls (33.1 ± 9.1). PD patients also had significantly lower scores than healthy controls on each of the four individual items, with item 4 being most significantly ($P < 0.001$) reduced in PD patients (Fig. 1). Low total scores for symptoms of nocturnal restlessness, which is indicative of increased symptom severity, correlated significantly with overall quality of nighttime sleep ($r = 0.48$, $P < 0.0001$), difficulty in falling asleep ($r = 0.40$, $P < 0.0001$), feeling tired and

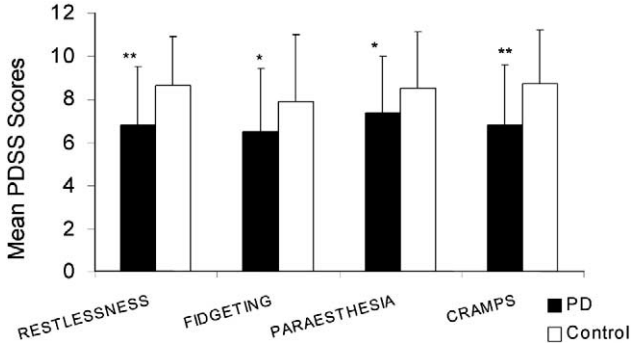

Fig. 1. Changes in mean (±SD) scores of four items (related to nocturnal restlessness) of Parkinson's Disease Sleep Scale (PDSS) in patients with Parkinson's disease and in healthy controls. *$P < 0.01$; **$P < 0.001$.

sleepy after waking ($r = 0.40$, $P < 0.0001$), and unexpectedly falling asleep during the day ($r = 0.2$, $P < 0.01$).

2.5. Discussion

The results of this study suggest that nocturnal restlessness of arms and legs, fidgeting, paresthesias, and painful muscle cramps affect patients with PD to a significantly greater extent than healthy adults. Furthermore, the severity of these symptoms correlates with reports of overall quality of nighttime sleep, difficulty in falling asleep, feeling tired and sleepy after waking, and propensity to fall asleep unexpectedly during the day. Interestingly, despite the identification of several PD patients who satisfy the criteria for diagnosis of RLS in this study, none carried this diagnosis prior to this survey. The response of restlessness to dopaminergic therapy, and to sustained dopaminergic therapy in particular, suggests that these problems may be secondary to effects of the protracted dopaminergic treatment. This indicates considerable underdiagnosis of RLS or nocturnal restlessness in PD.

3. Sustained dopaminergic treatment as it applies to RLS

The mainstay of treatment for RLS remains dopaminergic replacement therapy (Table 2), although published evidence is confounded by issues surrounding a lack of parallel group studies, recruitment bias within study populations, and a lack of studies in multi-ethnic and younger subjects [7]. There are 15 published studies (eight double-blind and seven clinical series) with relatively small numbers of patients (ranging from six to 32) of standard levodopa at doses varying from 100 to 600 mg [7]. The results of these studies suggest that levodopa therapy consistently reduces PLMS and nocturnal RLS symptoms in the early part of the night. However, augmentation is a problem that can occur after nocturnal dosing of levodopa. Augmentation may manifest as the occurrence of RLS symptoms earlier in the day after and/or the spread of RLS symptoms to the trunk or upper limbs [21–24]. Rebound phenomena, which are defined as a worsening of symptoms in the early morning after nocturnal dosing with levodopa, may also occur [23,24].

Dopamine agonists are used for RLS because of emerging problems such as augmentation related to long-term levodopa therapy. Several double-blind, single-blind, and open-label trials involving ergot (bromocriptine, pergolide, cabergoline) and non-ergot (pramipexole, ropinirole, apomorphine) dopamine agonists have been published [7]. Bromocriptine at a mean dose of 7.5 mg showed subjective benefit in 83.8% of cases with a particular effect on PLMS, although a comparative study with levodopa suggests better tolerability of levodopa [7]. Pergolide (0.1–0.75 mg) given in the evening as either a single dose or in two doses appears to have a sustained effect through the night with improvement of RLS symptoms, and it may have a preferentially better subjective improvement and a greater effect on PLMS (79 vs. 45%) in comparison to levodopa. While levodopa-induced augmentation may be reversed after treatment with pergolide, others have reported augmentation with pergolide [7,28]. (The article by Ferini-Strambi in this supplement further discusses the augmentation of RLS with dopamine agonists.) Beneficial effects on RLS with ropinirole (0.5–4 mg once or twice per day), dihydroergocriptine (10–40 mg in divided doses), pramipexole (1.5 mg single evening dose), cabergoline (1–2 mg evening dose), and apomorphine (nocturnal subcutaneous infusion of 18–48 mg) have been described [25–32]. Of these, pramipexole, ropinirole, and cabergoline have been examined in a double-blind fashion. Long-term (mean 7.8 months) efficacy of pramipexole (0.25–0.75 mg) suggests continued efficacy of pramipexole during the follow-up period [29].

Cabergoline, the longest-acting dopamine agonist with a half-life of 65 h, has the advantage of being active throughout the 24-h day when taken daily and has been found to be effective in the treatment of PD-related nocturnal disturbances [33]. This has been observed to be especially true

Table 2
Dopaminergic treatment strategies for RLS[a]

Drugs	Dose range (mg)	Specific issues
Levodopa DCI	100–600 (an evening or divided dose)	Rebound/augmentation[b]
Bromocriptine	7.5 (divided dose)	Poor tolerance
Pergolide	0.1–0.75 (single or two evening doses)	N/A
Ropinirole	0.5–4 (once or twice daily)	N/A
DHEC	10–40	
Pramipexole	1.5 (single evening dose)	N/A
Cabergoline	1–2	Useful for augmentation
Apomorphine	18–50/12 h (overnight s.c. infusion)	N/A
Amantadine	100–400	N/A
Piribedil	Unknown	Limited availability
Talipexole	Unknown	Only available in Japan

[a] DCI, decarboxylase inhibitor; DHEC, dihydroergocriptine; N/A, not applicable; s.c., subcutaneous.
[b] Should rebound or augmentation occur, longer-acting agonists such as cabergoline or continuous subcutaneous infusion of apomorphine may be appropriate.

when the drug is administered at night. We have observed in an open, parallel-group study that in comparison to levodopa/carbidopa, patients taking an evening dose of cabergoline rated their sleep quality and clinical global state to be improved by 88% compared to 27% with levodopa/carbidopa [33]. When compared to pergolide—another commonly-used dopamine agonist with a half-life of 7 to 16 h—cabergoline was more effective in reducing nocturnal waking, early morning dystonia, and dystonic pain in one treatment trial [34]. A small, multicenter, video-blinded crossover trial comparing cabergoline (up to 6 mg once a day) and pergolide (up to 5 mg daily given three times a day) reported similar motor improvement in both groups, although cabergoline was significantly more efficacious in improving motor scores related to the 'off' period after 8 weeks of treatment [35]. Analysis of results of a 5-year cabergoline versus levodopa monotherapy study indicate that the percentage of early morning akinesia (1.3%), an important cause of nocturnal disability and sleep disruption in PD patients, was significantly reduced in those receiving cabergoline in comparison to those receiving levodopa (5.5%) [36]. Open-label and double-blind studies suggest that cabergoline is well tolerated in patients with severe RLS who have failed other therapies in addition to those with augmentation [30]. In an ongoing natural history study, analysis of the records of over 30 patients with a diagnosis of both PD and RLS under follow-up at our center suggests that cabergoline is effective and well tolerated in the elderly and the young (unpublished observations). These observations highlight the importance of continuous dopaminergic stimulation in RLS.

The use of dopamine agonists is often avoided in elderly PD patients because of side effects such as confusion, hallucinations, and aggravation of postural hypotension. However, work by Shulman and colleagues [37] and our group [38] have challenged this view. Appiah-Kubi et al. have recently reported results of a follow-up study of 264 young and elderly (39–88 years of age) cabergoline-treated PD patients over a mean period of 2 years (range 0.5–12) [38]. Cabergoline monotherapy was used in the young (24 of 92 patients under 65 years) and the elderly (17 of 110 patients 65 years and over), and also as adjunctive therapy with daily doses of up to 8 mg. Using the Shulman et al. criteria for tolerability [37], cabergoline demonstrated excellent (>80%) and comparable tolerability in the young and the elderly. This was also true for some patients who were intolerant to other agonists.

4. Conclusions

In summary, RLS is a common condition with considerable morbidity that can present either as primary disease or secondary to other medical conditions. Its effect on the overall quality of life of the patient and the caregiver is unknown. RLS or RLS-type symptoms (nocturnal restlessness) occur in PD and require specific recognition and management. Whether RLS or nocturnal restlessness is secondary to the disease process of PD or to dopaminergic therapy for PD remains to be ascertained. A high index of suspicion is required for prompt diagnosis, counselling, and ensuring that patients are adequately treated.

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