

**VIEWPOINT**

Does Restless Legs Syndrome Have a Different Pathomechanism in Premotor and Motor Parkinson's Disease?

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INTRODUCTION

There is a long-standing debate regarding the comorbid association of Parkinson's disease (PD) and restless legs syndrome (RLS) in the same patients. Recently, many studies have been focused mainly on the differentiation of the RLS cooccurring with PD from the primary form of the sensory-motor disorder,¹ whereas possible heterogeneity in the pathomechanisms of RLS related to the timing of its onset in respect to the clinically overt PD and the so-called premotor/prodromal PD remains as yet unexplored. This issue is directly connected to the hitherto unresolved question concerning whether RLS is a risk factor for the subsequent development of PD or vice versa. In most cross-sectional studies aimed at assessing the prevalence of RLS in PD, it has been reported retrospectively that in more than two-thirds of the patients on average, this sensory-motor disorder had emerged in the motor phase of the neurodegenerative disease, when almost all patients were receiving ongoing dopaminergic (DAergic) therapy.¹ Therefore, only approximately 25%–30% of RLS appears before the onset of motor symptoms/signs of PD, i.e., in the premotor phase, and this figure is consistent with the lack of difference in RLS prevalence found between newly diagnosed, previously untreated PD patients and age-matched controls.^{2,3} This unbalanced prevalence of RLS onset between the premotor and motor phases of PD raises the question that different pathomechanisms might underlie RLS depending on the timing of its onset.

RLS DEVELOPING IN THE PREMOTOR PHASE OF PD

Only two studies have prospectively investigated the subsequent occurrence of PD in subjects with prevalent RLS. Although all the known comorbidities associated with RLS and RLS mimics had not been excluded, a higher incidence of PD mainly in male subjects with pre-existing RLS compared to the control group without RLS was found during a median follow-up period of 4 and 7.8 years, respectively, suggesting that this sensory-motor disorder may be a risk factor or more likely an early feature of PD.^{4,5} Indirect support for this view has been provided by a more recent longitudinal study showing a positive, although moderate, association between persistent/recurrent RLS and symptoms/signs currently regarded as prodromal of PD in men, such as rapid eye movement sleep behavior disorder (RBD) and constipation.⁶ However, this finding does not explain whether RLS and PD are linked by a common pathomechanism and whether the pathomechanism involved in RLS occurring in the setting of PD differs from that of primary RLS. In this context, decreased intraepidermal small fiber density⁷ and impairments in thermal somatosensory function in the lower limbs⁸ in subjects with idiopathic RBD led to the hypothesis of the possible involvement of cutaneous sensory small fibers, as a condition intrinsic to the neurodegenerative process in Lewy body disease, in the pathomechanism of RLS emerging in the premotor phase of PD. This hypothesis has been corroborated by recent findings on skin biopsies

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showing a decrease in intraepidermal somatosensory unmyelinated C fiber density in the lower limbs with a non-length dependent pattern in four patients with late-onset RLS that developed in the premotor phase of PD in the absence of large fiber damage.⁹ Although an incidental cooccurrence of RLS and small fiber pathology cannot be completely excluded in these PD patients, this finding may represent the first report of the association of RLS with PD-related distal somatosensory axonopathy, providing support to the concept that RLS may be an intrinsic early prodromal feature of PD rather than a risk factor, as has been previously proposed.^{4,5} The exclusion of known secondary causes of both RLS and small fiber pathology in the same patients supports this view.⁹ The non-length-dependent pattern found on skin biopsy is indicative of involvement of small neurons located in the somatosensory dorsal root spinal ganglia, consistent with sensory neuronopathy, which could represent the counterpart of that found in the peripheral sympathetic ganglia in 50% of incidental Lewy body disease cases believed to represent the premotor phase of PD.¹⁰ However, whether small fiber pathology with a non-length dependent pattern characterizes only RLS predating the onset of motor PD remains to be established and deserves further investigation, since it cannot be excluded that the same pathomechanism may also be involved in the development of RLS in the motor phase of PD. Overall, these data support the view that the impairments in somatosensory epidermal C fibers may occur early in the neurodegenerative process and, thereby, enlarge the spectrum of small fiber dysfunction in the prodromal phase of PD that, to date, is believed to affect nearly exclusively the autonomic sympathetic terminal axons, mainly in the cardiovascular system.¹¹ If this finding is confirmed in a larger population of patients, intraepidermal somatosensory small fiber pathology should be regarded to underlie most cases of RLS emerging in the premotor phase of PD, supporting its “peripheral” origin. Considering the low estimated occurrence of RLS onset in the premotor phase of PD, it is expected that not all somatosensory small fiber pathology intrinsic to PD detected in this phase will be associated with RLS.

RLS EMERGING IN THE MOTOR PHASE OF PD

In contrast, a significantly increased prevalence of RLS in patients with fully developed PD receiving chronic DAergic medication compared to newly diagnosed previously untreated patients and to age-matched controls has been found.¹² An increased incidence of RLS in PD patients receiving chronic DAergic treatment in comparison to the general population¹³ has also been found. In line with the results of these studies, it had been previously reported by Lee et al.¹⁴ that the occurrence of RLS in PD

patients was correlated with the duration of DAergic treatment but not with the daily dosage of the same drugs. Taken together, these findings, which are clearly at odds with the well-known symptomatic relief produced by DAergic drugs in primary RLS, indirectly suggest that in patients with clinically overt PD this sensory-motor disorder may have a pathomechanism different from that underlying the primary form and possibly from the RLS emerging in premotor PD. Under these circumstances, the postulated pathomechanism underlying the increased prevalence/incidence of RLS in PD patients receiving chronic DAergic therapy may be related to dysfunction of the DAergic A11 area in the posterior hypothalamus, the site of origin of the descending diencephalospinal pathway,¹⁵ which has been reported to become involved in PD-related neuronal pathology in Braak’s stage III of the disease,¹⁶ causing a state of denervation hypersensitivity of postsynaptic DA receptors in the spinal cord. As a consequence, the chronic stimulation of DA receptors by DAergic drugs at the dosage employed in PD patients may produce a further increase in their hypersensitivity, in turn inducing an increased occurrence of RLS by unmasking subclinical or latent forms, possibly through an “augmentation-like” mechanism. This effect ultimately provides the major determinant contribution to the comorbid association between the two disorders. If this hypothesis is correct, then the sensory-motor disorder emerging in the motor phase of PD should be considered “centrally” mediated and DA-dependent.

CONCLUSIONS

On the basis of these concepts, RLS in the setting of PD should be regarded as a heterogeneous disorder likely due to the different pathomechanisms, i.e., “peripherally” or “centrally” mediated, underlying its development depending on whether onset occurs in the premotor or motor phase of PD. Therefore, if the epidermal somatosensory small fiber neuropathy/pathology occurring in the premotor phase is an integral part of PD, a mutual relationship linking RLS and PD may be recognized. The RLS predating the clinical diagnosis of PD should represent an intrinsic sleep disturbance and an early prodromal, although relatively infrequent, feature of PD. In contrast, PD should represent a predisposing or risk condition for RLS to develop with high frequency in the motor phase of this neurodegenerative disease, for which additional triggering factors, such as chronic DAergic therapy, need to be implicated.¹³ If this hypothesis is correct, then it is expected that the two subtypes of RLS emerging in premotor and motor PD may show different clinical phenotypes and courses and possibly different therapeutic responses. In the case of RLS associated with somatosensory small fiber pathology, the clinical picture would be characterized by concurrent painful/dyesthetic sensory symptoms, although it has been reported that only

a limited proportion of PD patients with decreased intraepidermal small fiber density in the lower limbs complain of neuropathic symptoms.¹⁷⁻¹⁹ The natural course of RLS would be dependent mainly on the progressive impairment of unmyelinated C fibers, possibly mimicking that occurring in small fiber pathology associated with other disease conditions. In contrast, the sensory-motor disorder emerging in PD patients receiving chronic DAergic therapy is usually mild and may show a course with a gradual reduction in frequency compared to that of primary RLS occurring in the general population,¹ as shown in a follow-up study,¹² possibly due to the development of progressive postsynaptic DA-receptor desensitization during long-term DAergic therapy.

Regarding the therapeutic response, the neuropathic PD-related subtype of RLS should be relieved by DAergic drugs, as recently shown in RLS associated with peripheral neuropathy in patients with type 2 diabetes,²⁰ and refractory forms of RLS should be relieved by alpha-2 delta ligands or opioids. In contrast, the supposed centrally generated RLS associated with chronic DAergic medication would be ameliorated mainly by reducing the daily dosage of these drugs, but such a practice is unfeasible on clinical ground due to the potential worsening of motor symptoms of PD, unless the patients undergo deep brain stimulation. Therefore, although specific pharmacotherapeutic guidelines for treating RLS in PD patients have not yet been established, it is advisable to take into account the postulated heterogeneous pathomechanisms underlying RLS based on the timing of its onset, i.e., in the premotor or motor phase of PD.

In conclusion, if the pathomechanisms postulated to be involved in RLS comorbid with PD are confirmed by further investigations in a larger population of patients, this sensory-motor disorder, depending on its time of onset, should be included in the list of sleep-related prodromal features of PD or to be regarded as secondary to PD itself and induced at an increased frequency rate by chronic DAergic therapy in the motor phase. Clinically, on the basis of the findings of skin biopsy in our study, in subjects developing a late-onset possible “primary” RLS, an epidermal somatosensory small fiber pathology should be considered. If small fiber involvement is ascertained by skin biopsy after the exclusion of known secondary causes of distal axonopathy, it would be advisable to carefully search for concurrent prodromal features of PD, such as RBD, constipation and hyposmia, and to track the onset of clinical motor signs/symptoms for the early detection of PD.

Ethical Statement

Not applicable.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

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REFERENCES

1. Rijsman RM, Schoolderman LF, Rundervoort RS, Louter M. Restless legs syndrome in Parkinson's disease. *Parkinsonism Relat Disord* 2014;20 Suppl 1:S5-S9.
2. Angelini M, Negrotti A, Marchesi E, Bonavina G, Calzetti S. A study of the prevalence of restless legs syndrome in previously untreated Parkinson's disease patients: absence of co-morbid association. *J Neurol Sci* 2011;310:286-288.
3. Gjerstad MD, Tysnes OB, Larsen JP. Increased risk of leg motor restlessness but not RLS in early Parkinson disease. *Neurology* 2011;77:1941-1946.
4. Wong JC, Li Y, Schwarzschild MA, Ascherio A, Gao X. Restless legs syndrome: an early clinical feature of Parkinson disease in men. *Sleep* 2014;37:369-372.
5. Szatmari S Jr, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovacs CP, Molnar MZ. Association of restless legs syndrome with incident Parkinson's disease. *Sleep* 2017;40:zsw065.
6. Iwaki H, Hughes KC, Gao X, Schwarzschild MA, Ascherio A. The association between restless legs syndrome and premotor symptoms of Parkinson's disease. *J Neurol Sci* 2018;394:41-44.
7. Schrempf W, Katona I, Dogan I, Felbert VV, Wienecke M, Heller J, et al. Reduced intraepidermal nerve fiber density in patients with REM sleep behavior disorder. *Parkinsonism Relat Disord* 2016;29:10-16.
8. Strobel AV, Tankisi H, Finnerup NB, Fuglsang-Frederiksen A, Jennum P, Svendsen KB, et al. Somatosensory function is impaired in patients with idiopathic REM sleep behaviour disorder. *Sleep Med* 2018;42:83-89.
9. Calzetti S, Bellanova ME, Negrotti A, Saccani E, Capozzi A, Pietrini V. Non-length-dependent somatosensory small fiber pathology presenting with restless legs syndrome in pre-motor Parkinson's disease. Evidence from skin biopsy in four patients. *J Clin Neurosci* 2019;69:139-142.
10. Adler CH, Beach TG. Neuropathological basis of nonmotor manifestations of Parkinson's disease. *Mov Disord* 2016;31:1114-1119.
11. Del Tredici K, Braak H. Lewy pathology and neurodegeneration in premotor Parkinson's disease. *Mov Disord* 2012;27:597-607.
12. Marchesi E, Negrotti A, Angelini M, Goldoni M, Abrignani G, Calzetti S. A prospective study of the cumulative incidence and course of restless legs syndrome in de novo patients with Parkinson's disease during chronic dopaminergic therapy. *J Neurol* 2016;263:441-447.
13. Calzetti S, Angelini M, Negrotti A, Marchesi E, Goldoni M. A long-term prospective follow-up study of incident RLS in the course of chronic DAergic therapy in newly diagnosed untreated patients with Parkinson's disease. *J Neural Transm* 2014;121:499-506.
14. Lee JE, Shin HW, Kim KS, Sohn YH. Factors contributing to the development of restless legs syndrome in patients with Parkinson disease. *Mov Disord* 2009;24:579-582.
15. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. *Neurology* 2006;67:125-130.
16. Jellinger KA. A critical evaluation of current staging of α -synuclein pathology in Lewy body disorders. *Biochim Biophys Acta* 2009;1792:730-

- 740.
17. Donadio V, Incensi A, Leta V, Giannoccaro MP, Scaglione C, Martinelli P, et al. Skin nerve α -synuclein deposits: a biomarker for idiopathic Parkinson disease. *Neurology* 2014;82:1362-1369.
 18. Lin CH, Chao CC, Wu SW, Hsieh PC, Feng FP, Lin YH, et al. Pathophysiology of small-fiber sensory system in Parkinson's disease: skin innervation and contact heat evoked potential. *Medicine (Baltimore)* 2016;95:e3058.
 19. Nolano M, Provitera V, Manganelli F, Iodice R, Stancanelli A, Caporaso G, et al. Loss of cutaneous large and small fibers in naive and L-dopa-treated PD patients. *Neurology* 2017;89:776-784.
 20. Harashima S, Nishimura A, Osugi T, Wang Y, Liu Y, Takayama H, et al. Restless legs syndrome in patients with type 2 diabetes: effectiveness of pramipexole therapy. *BMJ Support Palliat Care* 2016;6:89-93.