

Impulse-Control Disorders and Restless Legs Syndrome in Parkinson's Disease: Are they Close Together or Far Apart?

Parkinson's disease (PD) is a neurodegenerative disorder, commonly affecting those above the age of 60 years. Nigrostriatal degeneration appears the primary pathology, with several other motor and non-motor circuits also getting involved, thereby, resulting in a myriad of motor and non-motor symptoms.^[1] Although symptomatic therapy using dopaminergic agents, primarily levodopa and dopamine agonists, remain the mainstay of treatment of PD, these therapies may result in several adverse-effects, with impulse control disorders (ICDs) being one of them.^[2]

ICDs are behavioral disorders characterized by a person's inability to control their "temptation" or "urge" to engage in pleasurable activities, along with impulsivity, compulsive repetition, and a disregard for potential harmful consequences of such behaviors.^[2] Previous studies evaluating the ICDs in PD patients reported a prevalence of up to 14%.^[3,4] However, Indian studies have reported at least one ICD in more than two-fifth of PD patients.^[5,6] The differences in the prevalence could be related to variations in socio-cultural, genetic, and environmental factors, the screening questionnaire used, as well as inclusion of some ICDs not classified elsewhere.^[6] The risk of developing ICDs increases with disease duration, further highlighting the role of dopaminergic therapy in its causation.^[2] Previous studies have identified several risk factors other than a higher dose of dopaminergic agents for developing ICDs among PD patients, including young age at onset, male gender, depression, personal/family history of addictive behaviors, and genetic influences (i.e., polymorphisms in dopaminergic, glutamatergic, serotonergic and opioid receptors).^[2,6-8]

Restless legs syndrome (RLS) is one of the neurological disorders reported more frequently in patients with PD. RLS manifest with an urge to move the limbs, usually associated with abnormal sensations in those limbs, with no other apparent secondary cause like cramps or neuropathy. The symptoms may worsen with rest and are more apparent in the evening or night time, with patients often moving the limbs or getting up to walk around to get partial or complete relief.^[9] The "urge" to move the limbs may be brought on by motor impulsivity. The prevalence of RLS in PD patients may vary from 1.6-38.3%.^[10] RLS prevalence rises as PD duration progresses, indicating a possible connection with progressive neurodegeneration and dopamine depletion.^[11,12] Although dopaminergic therapies may improve the RLS symptoms, it has been contemplated that they may play a role in the development of RLS in PD patients.^[11]

Therefore, RLS and ICDs appear to lie at the opposite ends with respect to the dopamine metabolism, as the former requires dopamine treatment while the latter is brought on

by an excess of dopamine. Reports of ICDs in one-fifth of untreated PD patients and addictive gambling in treatment naive idiopathic RLS patients, raises the possibility that ICDs and RLS might have a common disease-specific patient profile, besides dopaminergic therapy.^[13,14] There is a dearth of studies determining whether the emergence of these two behaviors is connected to the neurodegenerative process of PD or they are separate issues precipitated by dopaminergic dysfunction.

Studies involving Western and Asian populations have reported several ICDs including pathological gambling, excessive buying, hypersexuality, binge eating, excessive engagement in hobbies, punting, dopamine dysregulation syndrome (DDS), and other unidentified behavioral disorders.^[5,6,15] To date, a single cross-sectional study reported a higher prevalence of ICDs in PD patients with RLS than those without it. It was significantly associated with a higher age, longer disease duration, and dopaminergic treatment.^[16] Moreover, they hypothesized that PD patients with RLS could develop a particular pattern of dopaminergic denervation involving the paraventricular nucleus of thalamus and its projections to the reward center, nucleus accumbens, thereby, enhancing the risk of ICDs in these patients.

In this issue of the journal, Birinder *et al.*^[17] have performed a single-center, observational cross-sectional study at a tertiary care hospital in North India to assess types and frequency of ICDs in PD and to evaluate the relationship, if any, between presence of RLS and ICDs. In addition, they also studied whether PD patient manifesting both RLS and ICDs had any significant psycho-behavioral profile. Of the 105 PD patients, 60 (57.1%) were males, with a mean age of 61.7 (± 9.6) years, mean disease duration was 4.8 years (range: 2-10 years), median H and Y stage was 3 (range: 1-4), and 15 (14.3%) patients had a substance abuse history. Nearly, all patients were taking dopaminergic therapy, with more than three-fifth patients on levodopa therapy alone. RLS was diagnosed in 18 (11.7%) patients. Using a validated scale, questionnaire for impulsive-compulsive disorders in Parkinson's Disease (QUIP), at least one ICD was observed in 51 (48.1%) PD patients, with compulsive medication use (47.4%) being most commonly reported, followed by compulsive eating (29.4%), compulsive buying (17.6%), pathological gambling (11.7%), and hyper-sexuality (3.9%). Nearly, 30% patients had other compulsive behaviors including reading, excessive internet use, listening to music, watching television, stitching, and arranging flowers in pots. Of the 18 PD patients having RLS, 12 (66.7%) had at least one ICD. The profile of ICDs in PD patients having both ICD and RLS was different from those without either ICD or RLS, with a higher prevalence of compulsive eating (44%) and

pathological gambling (27.8%) in the former. Compulsive eating was more prevalent nocturnally as was gambling, and was believed to disturb night sleep, thereby increasing chances of noticing RLS symptoms. Conversely, poor sleep quality and excessive daytime somnolence resulting from RLS might have precipitated nocturnal impulsivity in PD patients with RLS, as documented by Scullin MK *et al.*^[18] As compared to PD patients without RLS or ICDs, those having both RLS and ICDs had a longer disease duration and greater levodopa equivalent daily dose.

Circadian variation in dopamine release has been reported, with sleep being promoted by activation of inhibitory D2 receptors during the night and predominant excitation of D1 receptors during daytime causing wakefulness.^[11] Similarly, the dose of dopaminergic agents may have a sleep-wake effect, with low dopaminergic dose stimulating D2-like receptors and precipitating sleep and a higher dose causing wakefulness by activating D1-like receptors.^[11] Moreover, worsening nigro-striatal dopaminergic deficiency in advanced PD may cause denervation hypersensitivity of D1 and D2 receptors, predominantly located in dorsal striatum. In addition, dopaminergic therapy may aggravate downregulation of dopamine receptors, thereby, increasing the need of dopamine whose release is already reduced in the night time and thus causing worsening of RLS symptoms.^[11] This cycle of dopamine deficiency on a relative hyper-dopaminergic state along with the circadian variability of endogenous dopamine and the ongoing neurodegenerative process in PD may contribute toward co-occurrence of RLS and ICDs. Thus, it may be inferred that ICDs and RLS in PD may share a common pathology, with RLS appearing to be a “motor ICD,” as reported by Marques A *et al.*^[19]

Hence, the emergence of RLS and ICDs in PD may be caused by a long-term dopaminergic therapy coupled to the neurodegenerative process itself. Results from future case-control studies with a larger sample size may enhance our understanding in this regard. Moreover, future studies may clear the role of substance abuse in developing ICDs and the relation between RLS augmentation and ICDs in patients with PD.

Ishita Desai, Niraj Kumar¹

Department of Neurology, Teerthanker Mahaveer University Hospital, Moradabad, Uttar Pradesh, ¹Department of Neurology and Division of Sleep Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Address for correspondence: Dr. Niraj Kumar,
Department of Neurology, All India Institute of Medical Sciences, Rishikesh,
Uttarakhand, India.
E-mail: drnirajkumarsingh@gmail.com

REFERENCES

- Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. *Can Med Assoc J* 2016;188:1157-65.
- Weintraub D, Claassen DO. Impulse control and related disorders in Parkinson's disease. *Int Rev Neurobiol* 2017;133:679-717.
- Antonini A, Barone P, Bonuccelli U, Annoni K, Asgharnejad M, Stanzione P. ICARUS study: Prevalence and clinical features of impulse control disorders in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2017;88:317-24.
- Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, *et al.* Impulse control disorders in Parkinson disease. *Arch Neurol* 2010;67:589-95.
- Sharma A, Goyal V, Behari M, Srivastva A, Shukla G, Vibha D. Impulse control disorders and related behaviours (ICD-RBs) in Parkinson's disease patients: Assessment using “questionnaire for impulsive-compulsive disorders in Parkinson's disease” (QUIP). *Ann Indian Acad Neurol* 2015;18:49-59.
- Paul B, Singh G, Bansal N, Singh G, Paul G. Gender differences in impulse control disorders and related behaviors in patients with Parkinson's disease and its impact on quality of life. *Ann Indian Acad Neurol* 2020;23:632-7.
- Lawrence AJ, Blackwell AD, Barker RA, Spagnolo F, Clark L, Aitken MR, *et al.* Predictors of punding in Parkinson's disease: Results from a questionnaire survey. *Mov Disord* 2007;22:2339-45.
- Erga AH, Dalen I, Ushakova A, Chung J, Tzoulis C, Tysnes OB, *et al.* Dopaminergic and opioid pathways associated with impulse control disorders in Parkinson's disease. *Front Neurol* 2018;9:109.
- Rizek P, Kumar N. Restless legs syndrome. *Can Med Assoc J* 2017;189:E245.
- Yang X, Liu B, Shen H, Li S, Zhao Q, An R, *et al.* Prevalence of restless legs syndrome in Parkinson's disease: A systematic review and meta-analysis of observational studies. *Sleep Med* 2018;43:40-6.
- Ferini-Strambi L, Carli G, Casoni F, Galbiati A. Restless legs syndrome and Parkinson disease: A causal relationship between the two disorders? *Front Neurol* 2018;9:551.
- Moccia M, Erro R, Picillo M, Santangelo G, Spina E, Allocca R, *et al.* A four-year longitudinal study on restless legs syndrome in Parkinson disease. *Sleep* 2016;39:405-12.
- Smith KM, Xie SX, Weintraub D. Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2016;87:864-70.
- Castrioto A, Funkiewiez A, Debù B, Cools R, Lhommée E, Ardouin C, *et al.* Iowa gambling task impairment in Parkinson's disease can be normalised by reduction of dopaminergic medication after subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2015;86:186-90.
- Molde H, Moussavi Y, Kopperud ST, Erga AH, Hansen AL, Pallesen S. Impulse-control disorders in Parkinson's disease: A meta-analysis and review of case-control studies. *Front Neurol* 2018;9:330.
- Marques A, Figorilli M, Pereira B, Derost P, Debilly B, Beudin P, *et al.* Impulse control disorders in Parkinson's disease patients with RLS: A cross sectional-study. *Sleep Med* 2018;48:148-54.
- Birinder PS, Aggarwal S, Paul G, Khehra AS, Jain A. Impulse-Control Disorders and Restless Leg Syndrome in Parkinson's Disease: Association or Coexistence. *Ann Indian Acad Neurol* 2023;26:161-6.
- Scullin MK, Sollinger AB, Land J, Wood-Siverio C, Zanders L, Lee R, *et al.* Sleep and impulsivity in Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:991-4.
- Marques A, Figorilli M, Lambert C, Pereira B, Vidal T, Montplaisir J, *et al.* The urge to move: From restless legs syndrome to impulse control disorders in Parkinson's disease. *J Sleep Res* 2021;30:e13127.

Submitted: 22-Feb-2023 **Accepted:** 23-Feb-2023

Published: 11-Apr-2023

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

DOI: 10.4103/aian.aian_166_23