Case Report/Case Series

Restless Genital Syndrome in Parkinson Disease

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IMPORTANCE Symptoms in the genital region, such as pain, discomfort, tingling, and burning sensations, have rarely been reported in Parkinson disease (PD), and the previous cases were attributed to nonmotor off symptoms. We report a patient with PD and severe genital discomfort unrelated to motor fluctuations but compatible with restless genital syndrome.

OBSERVATIONS A 65-year-old woman with PD experienced a disabling discomfort in her pelvis and genital region for 3 years. The episodes occurred in the evening and were triggered by sitting or lying down for a period. Gynecological investigation was unrevealing. She experienced improvement with a low dose of a dopamine agonist.

CONCLUSION AND RELEVANCE Restless genital syndrome is a rare disorder that can be a source of distress and disability. In patients with PD, restless genital syndrome should be included in the differential diagnosis of genital symptoms and restlessness, along with nonmotor wearing off and akathisia. A detailed clinical history is essential for this diagnosis and treatment with dopamine agonists can provide benefit.

JAMA Neurol. 2014;71(12):1559-1561. doi:10.1001/jamaneurol.2014.1326
Published online October 6, 2014.

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Genital symptoms are rarely reported in Parkinson disease (PD); however, when present, these are often severe and unrelenting, becoming the main source of disability.[1] Either male or female patients can be affected and, in most cases, the genital symptoms are subjectively described as a discomfort, pain, numbness, vibration, restlessness, or burning sensation involving the vagina, perineum, pelvis, and proximal portion of the lower limbs. Similar symptoms have been reported in drug-induced parkinsonism (tardive pain),[2] atypical parkinsonian syndromes,[1] and otherwise healthy individuals.[3] In patients with PD, the genital discomfort has been attributed to wearing-off nonmotor fluctuations and dopaminergic denervation.[4]

In patients without PD, a syndrome of persistent sexual arousal was described in 2001.[5] The clinical criteria for this were defined as an involuntary genital arousal that persists for an extended period (hours to months), does not go away with 1 or more orgasms, is unrelated to feelings of sexual desire, is intrusive and unwanted, and is associated with significant distress.[6] The pathogenesis had been speculated by several authors until 2009, when preexisting or coexisting restless leg syndrome (RLS) was found in 12 of 18 patients and the term *restless genital syndrome* (RGS) was introduced.[3] Therapeutic approaches have included clonazepam, oxazepam, tramadol hydrochloride, antidepressants, estrogens, psychotherapy, transcutaneous electrical nerve stimulation, and even clitoridectomy,[3] with poor results.

We report a patient with PD and severe genital discomfort unrelated to motor fluctuations but with a clear circadian rhythm and response to pramipexole, compatible with RGS. Our goal is to highlight the responsiveness of RGS to dopamine agonists (DAs) and to discuss the complexity of the differential diagnosis of genital symptoms in PD, which can be a source of misdiagnosis and inappropriate investigation and treatment. The patient provided written informed consent for this case report.

Report of a Case

A 65-year-old woman presented to our clinic with PD since the age of 60 years, beginning with resting tremor in the left hand, gradually progressing to the left lower limb. She denied balance, cognitive, and autonomic disturbances. She had experienced discomfort in her pelvis and genital region for 3 years, reported as a sensation of "congestion," itching, and "growing" of pelvic organs, suddenly spreading to her thighs resulting in a "jolt." The episodes occurred daily, only during the evening and night, and were triggered by sitting or lying down for a period. Her sleep was markedly disrupted by the genital discomfort, which could only be relieved by physical activities, standing, or walking. There was no restlessness in the legs. She had been taking levodopa/carbidopa, 100/25 mg 3 times a day, with meals for approximately 3 years, with improvement of PD but persistence of the genital symptoms. She had developed motor fluctuations characterized by worsening of the tremor and slowness with an end-of-dose pattern but with no appearance of the genital discomfort. Repeated gynecological evaluations were normal and hormonal replacement with estrogen had been ineffective. Hematologic parameters and investiga-

Box. Previous Nomenclatures Applied to RGS

- Vulvodynia
  - Vulvar dysesthesia
  - Male genital skin pain
  - Penoscrotodynia
  - Persistent sexual arousal syndrome
  - Persistent genital arousal disorder

Abbreviation: RGS, restless genital syndrome.

tion findings for neuropathy with vitamin B_{12}, folic acid, glucose, hemoglobin A_{1c}, and protein immunoelectrophoresis were normal. A polysomnography revealed only 1.7 hours of total sleep, with vocalizations, but no periodic limb movements in sleep, which had been used to argue against a diagnosis of RLS.

Her prior diagnoses included akathisia, hyperesthesia, neuropathic pain, and, more recently, persistent sexual arousal syndrome, with no consideration of an association with RLS. Duloxetine hydrochloride, 30 mg, worsened her symptoms, whereas oxazepam, 15 mg, was only temporarily effective. Based on the clear circadian rhythm, onset with resting and relief with activity, RGS was considered. A trial of pramipexole, 0.25 mg, at night improved the genital discomfort within a few days, with sustained benefit over the subsequent 9 months. However, the motor fluctuations became refractory to increments in therapy, and we are considering deep brain stimulation.

Discussion

We present a patient with PD who developed disabling genital discomfort in the early disease stage. She had no atypical signs, and her PD was responsive to levodopa. Although she had motor fluctuations, her genital symptoms were unrelated to the wearing-off periods, consistently occurring in the evening and night after sitting or lying still. Her symptoms were very similar to those previously described in RGS and her dramatic response to pramipexole supports this diagnosis.[3,6,7]

The intrusive genital symptoms in RGS may be perceived as a discomfort, irritation, tingling, itching, congestion, and pain. Although most patients have difficulty describing their symptoms,[3] the account is very similar among patients, reinforcing the organic nature of this disorder.[6,7] In addition, there are similarities among RGS, tardive genital pain,[2] and genital pain in PD,[1,4,8] suggesting a possible dopaminergic mechanism. A variety of terms have been applied to patients with otherwise unexplained genital discomfort (**Box**).[3,7,9] However, it has been suggested that the underlying process in all of these is the same, and unifying the nomenclature under the term *RGS* has been proposed.[7]

Neurovascular dysfunction, pelvic varicosities, and vasocongestion have been suggested as pathogenic mechanisms in RGS[3]; however, these are challenged by the widespread finding of pelvic varicosities on ultrasonography of asymptomatic women. The observation that RGS exacerbates during sleep and that 87% of patients experience worsening while sitting have led to the hypothesis that such positions aggravate pelvic congestion or provoke neural compression.[3] In our opinion, these features support RGS as a phenotype of RLS.[3,9] In keeping with this, augmentation[10] and response to spinal cord stimulation have been described in vulvodynia[11] and likewise in RLS.

Neuropathy, hyperesthesia, and allodynia have also been claimed as possible mechanisms for RGS.[3,7] In our case, duloxetine, an antidepressant typically used for neuropathic pain, exacerbated the symptoms, as expected in RLS. Currently, RGS is considered a disorder of somatosensory function rather than a sexual dysfunction, thus the clinical criteria should be redefined.[7]

There are an increasing number of reports of restlessness affecting body parts, either in isolation or in association with RLS, including the genital region,[3,9] bladder,[12] and abdomen.[13] Of note, 67% of RGS cases coexist with RLS and overactive bladder.[3] Despite this, the essential diagnostic criteria for RLS remain limited to leg involvement: an urge to move it preceded by a discomfort, worsened by inactivity and diminished by movement, all with a circadian rhythm. Dopamine agonists are first-line therapy for RLS; however, they have been underused in RGS owing to the poor recognition of this association.

The prevalence of RLS in PD has been estimated at 24%.[14] To our knowledge, this is the first report of RGS in a patient with PD. Our patient was disabled by the genital discomfort and her sleep was profoundly impaired, as revealed by the polysomnography. The absence of periodic limb movements in sleep had been used as an argument against her symptoms being related to RLS but the lack of gynecological abnormalities, the clinical presentation, and response to low doses of DA supported this diagnosis. Withdrawing pramipexole or performing a trial with opioids to confirm our opinion could not be justified on ethical grounds in light of the profound discomfort she experienced before the treatment.

In our patient, the symptoms were unrelated to nonmotor off or akathisia, occurring exclusively in the evening and night despite clear wearing off during the daytime. Moreover, the low dose of DA provided would have been insufficient to cause such benefit to nonmotor fluctuations. Differentiating between these diagnoses is relevant, especially in patients under consideration for deep brain stimulation. Subthalamic nucleus stimulation is known to improve PD motor fluctuations; however, RLS can improve,[15] worsen, or even emerge after deep brain stimulation, probably owing to reduction in dopaminergic therapy.[16]

Conclusions

In summary, RGS is a rare disorder that can be a source of distress and disability. In patients with PD, this should be included in the differential diagnosis of genital symptoms and restlessness, along with nonmotor off and akathisia. A detailed clinical assessment is essential for this diagnosis, and treatment with DA can be beneficial. Restless genital syndrome should be considered a phenotype of RLS, as should restless bladder and restless abdomen.[12,13] It is important to raise awareness of this disabling but treatable condition.

ARTICLE INFORMATION

Accepted for Publication: April 23, 2014.

Published Online: October 6, 2014. doi:10.1001/jamaneurol.2014.1326.

Author Contributions: Dr Lang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Aquino, Lang.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Aquino.
Critical revision of the manuscript for important intellectual content: Mestre, Lang.
Study supervision: Lang.

Conflict of Interest Disclosures: Dr Lang has served as an advisor for Abbvie, Allon Therapeutics, Avanir Pharmaceuticals, Biogen Idec, Boerhinger-Ingelheim, Ceregene, Medtronic, Merck, Novartis, NeuroPhage Pharmaceuticals, Teva, and UCB. Dr Lang has received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press and has served as an expert witness in cases related to the welding industry. No other disclosures were reported.

Funding/Support: Dr Aquino received a scholarship from CAPES Foundation, Brazil. Dr Lang has received grants from Brain Canada, Canadian Institutes of Health Research, Edmond J. Safra Foundation, Michael J. Fox Foundation, National Parkinson Foundation, Parkinson Society Canada, Tourette Syndrome Association, and W. Garfield Weston Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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