https://doi.org/10.1590/0004-282X-anp-2020-0122

ARTICLE

Is restless legs syndrome in Parkinson disease patients associated with any specific factor?

A síndrome das pernas inquietas nos pacientes com doença de Parkinson está associada a algum fator específico?

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ABSTRACT

Background: Restless legs syndrome or Willis-Ekbom disease is a disorder characterized by unpleasant sensations associated with the need to mobilize the lower limbs. In Parkinson disease patients, restless legs syndrome is associated with worse quality of life and excessive sleepiness. Regarding other factors, results of different studies are controversial. **Objective:** To determine the factors associated with the restless legs syndrome presence in Parkinson disease patients. **Methods:** A cross-sectional study was conducted in 88 consecutive Parkinson disease patients from the outpatient clinic for 21 months. Participants underwent a clinical interview, assessment based on standardized scales (Epworth Sleepiness Scale, Parkinson Disease Questionnaire – 39, Pittsburgh Sleep Quality Index, International Restless Legs Syndrome Study Group rating scale), and video-polysomnography. **Results:** Out of the 88 participants, 25 had restless legs syndrome. In the multivariate analysis, restless legs syndrome in Parkinson disease has been associated with the symptom of smell loss and quality of sleep and life. In the univariate analysis, restless legs syndrome in Parkinson disease has occurred more frequently in women with higher frequency of insomnia, constipation, and anosmia than in the group without restless legs syndrome. **Conclusion:** Restless legs syndrome is a prevalent condition in patients with Parkinson disease and is associated with specific characteristics in this group of patients.

Keywords: Parkinson Disease; Sleep; Restless Legs Syndrome.

RESUMO

Introdução: A síndrome das pernas inquietas, ou doença de Willis-Ekbom, é um transtorno caracterizado por sensações de desconforto associadas à necessidade de movimentar os membros inferiores. Nos pacientes com doença de Parkinson, a síndrome das pernas inquietas está associada a uma qualidade de vida inferior e sonolência excessiva. Em relação a outros fatores, resultados de diferentes estudos mostraram resultados controversos. **Objetivo:** Determinar os fatores associados à presença da síndrome das pernas inquietas nos pacientes com doença de Parkinson. **Métodos:** Um estudo transversal foi conduzido com 88 pacientes com doença de Parkinson, consecutivos, acompanhados em ambulatório especializado, durante 21 meses. Participantes passaram por uma entrevista clínica, avaliação por meio de escalas padronizadas (Escala de Sonolência de Epworth, Questionário de Qualidade de Vida da Doença de Parkinson, Índice de Qualidade de Sono de Pittsburgh, Escala de Gravidade Internacional da Síndrome das Pernas Inquietas) e videopolissonografia. **Resultados:** Do total de 88 participantes, 25 tinham síndrome das pernas inquietas. Na análise multivariada, a síndrome das pernas inquietas na doença de Parkinson esteve associada à perda de olfato, assim como à qualidade de vida e ao sono. Na análise univariada, a síndrome das pernas inquietas na doença de Parkinson ocorreu mais frequentemente em mulheres, com maior frequência de insônia, constipação e anosmia, do que no grupo sem síndrome das pernas inquietas. **Conclusão:** A síndrome das pernas inquietas é uma condição prevalente na doença de Parkinson e está associada a características específicas neste grupo de pacientes.

Palavras-chave: Doença de Parkinson; Sono; Síndrome das Pernas Inquietas.

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Conflict of interest: There is no conflict of interest to declare.

Authors' contributions: M.A. Sobreira-Neto - Conception, Organization, Execution; Statistical Analysis: Design, Execution, Review and Critique; Manuscript Preparation: Writing of the first draft, Review and Critique; M.A. Pena-Pereira - Research Project: Conception, Organization, Execution; Manuscript Preparation: Review and Critique; E.S.T. Sobreira - Research Project: Organization, Execution; Manuscript Preparation: Review and Critique; M.N.H. Chagas - Research Project: Conception, Organization, Execution; Manuscript Preparation: Review and Critique; C.M.O Almeida - Research Project: Conception, Organization; Manuscript Preparation: Review and Critique; R.M.F. Fernandes - Research Project: Conception, Organization; Manuscript Preparation: Review and Critique; V. Tumas - Research Project: Conception, Organization; Statistical Analysis: Review and Critique; Manuscript Preparation: Review and Critique; A.L. Eckeli - Research Project: Conception, Organization, Execution; Statistical Analysis: Design, Execution, Review and Critique; Manuscript Preparation: Writing of the first draft, Review and Critique.

Received on March 28, 2020; Received in its final form on June 11, 2020; Accepted on June 23, 2020.

INTRODUCTION

Restless legs syndrome (RLS) or Willis-Ekbom disease is a disorder characterized by the need to mobilize the lower limbs, which is sometimes associated with unpleasant sensations. RLS symptoms are partially or completely alleviated during this mobilization and they occur or worsen with rest and at night[1]. The onset of symptoms in RLS patients can occur throughout the patient's lifetime[2,3]. It often presents a chronic and progressive course, with periods of remission[4]. The association between increased prevalence of RLS and increased age has already been documented[5,6,7].

In the general population, Eckeli et al. showed a RLS lifetime prevalence of 6.4% in the city of Cássia dos Coqueiros in São Paulo State[8]. In Parkinson disease (PD) patients, studies estimate a prevalence in up to 50% of them. Some studies have showed a higher prevalence of RLS in PD patients compared to the Control Group[9,10,11,12,13,14]. This variability occurs because many conditions that mimic RLS symptoms, such as motor symptoms, cramps, polyneuropathy, positional discomfort, and akathisia, occur in PD patients.

RLS may result from an abnormal integration of sensory-motor pathways due to disinhibition at the spinal level caused by reduced activity of dopaminergic diencephalon-spinal pathways from the hypothalamus (A11 cells)[15]. In PD patients, these neurons degenerate together with nigrostriatal pathway neurons, which may justify a higher prevalence of RLS in PD patients[14]. In addition, dopaminergic medications are provided in order to treat PD motor and RLS symptoms, reinforcing the dopaminergic deficiency observed in both pathologies[14]. Finally, several studies indicate an iron deficiency in specific areas of the brain as a cause for RLS[16]. Two papers demonstrated an iron deficiency in PD patients with RLS compared to the ones without RLS[12,17].

Several investigations compared PD patients with and without RLS. However, the diversity of samples and results hampers definitive conclusions[14]. Furthermore, most studies showed RLS onset concomitant or after PD onset[18,19,20,21]. Patients with longer PD onset time and longer dopaminergic therapy time seem to have higher prevalence of RLS[22]. Some papers have also presented that more severe parkinsonism symptoms are related to a higher frequency of RLS symptoms[12,18,21,22]. Other studies showed that PD patients with RLS had worse sleep quality, higher excessive sleepiness, and worse quality of life than patients without RLS[9,18,20,21].

The problems related to RLS in PD patients are frequent, potentially serious, and possibly have important repercussions for the disease severity. Thus, the present research is important for a better understanding of these topics in PD patients. This study aimed to determine the factors associated with the presence of RLS in PD patients.

METHODS

Study design and population

A cross-sectional study was performed in PD patients from the tertiary outpatient clinic of Movement Disorders of Hospital das Clínicas, School of Medicine of Ribeirão Preto – University of São Paulo (HC-FMRP-USP), São Paulo, Brazil, for 21 months between February of 2010 and March of 2012.

In total, 124 consecutive individuals with PD were approached on their routine appointment. Ninety of these individuals provided an informed consent. Subsequently, the patients that agreed to participate underwent a clinical assessment with a psychiatrist and neurologists specialized in sleep medicine and movement disorders. Two individuals did not attend the polysomnography (PSG). Patients underwent polysomnography with a maximum interval of two weeks after the initial assessment. During this time, there was no change in drug treatment.

This study was approved by the Ethics Committee of HC-FMRP-USP, under the protocol number 13410, in accordance with the ethical principles of the Declaration of Helsinki.

Clinical evaluation

The clinical evaluation was based on standardized scales and assessment of sleep disorders, cognitive framework, motor, and psychiatric symptoms of PD. We asked the patients about some symptoms, such as: hypersalivation, dysphagia, dyskinesia, nocturia, anosmia, excessive sweating, and constipation.

The scales related to the quality of life and sleep used were Epworth Sleepiness Scale (ESS), Parkinson's Disease Questionnaire (PDQ-39), and Pittsburgh Sleep Quality Index (PSQI).

A neurologist specialized in sleep medicine performed a clinical evaluation to detect and diagnose sleep disorders according to the International Classification of Sleep Disorders – third edition (ICSD-3)[1,23].

The functional impairment was assessed by a neurologist specialized in movement disorders. The following scales were used: Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn & Yahr (H&Y) Parkinsonian Staging, and Schwab & England (S&E) activities of the daily living score. The Mini-Mental State Examination (MMSE) and Global Deterioration Score (GDS) were applied for cognitive assessment. Patients were evaluated during the best 'on' period as possible for motor and cognitive assessment. In addition, the International Restless Legs Syndrome Study Group rating scale (IRLS) was applied for evaluating the severity of RLS.

To achieve psychiatric diagnosis, following the criteria of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition), American Psychiatric Association (DSM-IV), a structured clinical interview for Axis I mental

disorders of the DSM-IV was used in the translated form that was adapted to Portuguese (SCID-I)[24].

Polysomnography

Time-synchronized video-PSG (v-PSG) was performed with a digital polygraph (computerized sleep system; Biologic Sleepscan VISION PSG, Natus Bio-logic Systems Inc., San Carlos, CA). Data were collected using an electroencephalogram — EEG (according to the International 10–20 System) (Fp1-M1, Fp2-M2, F3-M1, F4-M2, C3-M1, C4-M2, P3-M1, P4-M2, F7-M1, F8-M2, T3-M1, T4-M2, T5-M1, T6-M2, O1-M1, O2-M2, Fz-Cz, Cz-Pz), bilateral electrooculogram (E1-M2, E2-M1), electrocardiogram (modified V2 lead), and surface electromyography of the mental and submental muscles. Surface electrodes were placed on both anterior tibialis muscles, masseters, and extensors of fingers. Digital video was recorded by an infrared camera (Sony Ipela., CA) synchronized with the PSG data. Respiration was monitored as follows: airflow was measured by a nasal pressure transducer system (AcSleep 119, Biolink Medical, São Paulo, Brazil) and nasal and mouth thermocouple airflow sensor (Pro-Tech Services Inc., Mukilteo, WA); chest and abdominal efforts were measured by respiratory inductive plethysmographic belts (Pro-Tech zRIP module, Pro-Tech Services Inc.); arterial SaO_2 was measured by pulse oximetry (Netlink Headbox, Natus Bio-logic Systems Inc.); snoring sounds were measured using a snoring microphone; and body position was determined using a sensor (Netlink Body Sensor Position, Natus Bio-logic Systems Inc.). All of the technical parameters were performed by the AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specification (2007)[25].

Statistical analysis

Kolmogorov-Smirnov test was applied to determine the distribution type of the variables. Parametric tests such as Student's *t*-test or analysis of variance (ANOVA) were used for normal distribution variables, whereas nonparametric Mann-Whitney or Kruskal-Wallis test were applied for those without a normal distribution. Pearson's coefficient was used in the correlation analysis of numeric variables with a normal distribution, and Spearman's correlation coefficient, for the analysis of numerical variables without a normal distribution. The hypothesis tests were conducted to verify the nullity of the correlation coefficients. In the analysis of categorical variables into two or more groups, chi-square or Fisher's exact tests were used according to the expected frequency in cells. Linear regression analysis was performed to calculate the predictive coefficients for dependent quantitative variables. For the multiple correlation analysis, logistic regression analysis was used for binary categorical dependent variables. Microsoft Office Excel, IBM SPSS Statistics 19, and R 3.1.0 were used to construct and analyze the database.

RESULTS

A total of 31 individuals complained about unpleasant sensations associated with the need to mobilize their lower limbs. Of these patients, 25 were diagnosed with RLS, four had motor fluctuations with "off" periods at night, and two had symptoms compatible with cramps.

The mean IRLS values were 25.14±8.1, with a minimum value of 6 and a maximum of 37. Four subjects had mild intensity of RLS symptoms, five subjects presented moderate intensity, nine patients had severe severity, and 7 presented very severe gravity.

In the univariate analysis, a higher prevalence of women was observed in the RLS group. Furthermore, RLS patients had a high score in the PSQI and PDQ-39 scales compared to PD patients without RLS (Table 1). A moderate correlation

Table 1. Comparison of sociodemographic and clinical variables between groups of Parkinson disease patients with and without restless legs syndrome (n=88).

Variables	PD+RLS (n=25)	PD−RLS (n=63)	p-value
Age (years), mean±SD	61±9	61±12	0.95
Sex (% of male)	44.0	69.8	0.03
Schooling (years)	7±6	6±4	0.79
PD onset time (months), mean±SD	108±64	100±65	0.31
Equivalent dose of levodopa (mg), mean±SD	937±364	802±470	0.08
BMI, mean±SD	25±4	25±5	0.58
ESS, mean±SD	13±6	11±5	0.14
PSQI, mean±SD	12±4	8±4	0.000
PDQ-39, mean±SD	54.8±12.3	39.5±17.5	0.000
UPDRS-III, mean±SD	19±13	18±12	0.78
GDS, mean±SD	2±1.0	2±1.0	0.68
MMSE, mean±SD	24.8±3.8	24.1±4.2	0.61
Hoehn & Yahr, mean±SD	2±0.3	2±0.5	0.66
Schawb & England, mean±SD	82.0±12.0	84.0±16.0	0.26
Presence of RBD (%) (n=55)	85.0	70.9	0.25
Presence of OSAS (%)	64.0	61.9	1.0
Presence of insomnia (%)	80.0	46.0	0.004
Presence of Excessive Fragmentary Myoclonus (%)	56.0	61.9	0.63
Presence of bruxism (%)	4.2	8.1	1.0
Presence of ALMA and/or HFT (%)	12.0	12.7	1.0
Presence of PLM index >15 events/h (%)	28.0	12.7	0.11
Presence of depression (%)	36.0	25.4	0.43
Presence of psychotic disorder (%)	20.0	11.1	0.31

Continue...

Table 1. Continuation.

Variables	PD+RLS (n=25)	PD−RLS (n=63)	p-value
Presence of anxiety disorder (%)	28.0	11.1	0.10
Presence of hypersalivation (%)	12.0	3.2	0.14
Presence of dysphagia (%)	0	1.6	1.0
Presence of dyskinesia (%)	56.0	33.9	0.09
Presence of nocturia (%)	64.0	54.0	0.47
Presence of anosmia (%)	44.0	11.3	0.002
Presence of excessive sweating (%)	36.0	25.8	0.43
Presence of constipation (%)	60.0	35.5	0.05
Antidepressant use (%)	24.4	25.4	0.54
Dopaminergic agonists use (%)	55.4	54.8	0.55

*p<0.05. RBD: REM Sleep Behavior Disorder; PD: Parkinson disease; SD: standard deviation; OSAS: Obstructive Sleep Apnea Syndrome; RLS: restless legs syndrome; BMI: body mass index; PDQ-39: Parkinson's Disease Quality of Life – 39; UPDRS-III: Unified Parkinson Disease Rating Scale – part III; PSQI: Pittsburgh Sleep Quality Index; MMSE: Mini-mental state examination; ESS: Epworth Sleepiness Scale; GDS: Global Deterioration Scale; ALMA: alternate leg movement activation; HFT: hypnagogic foot tremor.

Table 2. Comparison of polysomnographic variables between groups of Parkinson disease patients with and without restless legs syndrome (n=88).

Polysomnographic variables	PD+RLS (n=25)	PD−RLS (n=63)	p-value
Total sleep time (h), mean±SD	5.0±1.5	4.9±1.4	0.91
Sleep efficiency (%), mean±SD	66.6±19.5	67.0±19.5	0.91
WASO (min), mean±SD	143.3±91.0	125.1±68.4	0.66
WAFA (min), mean±SD	9.2±14.3	12.9±21.7	0.55
Sleep onset latency (min), mean±SD	22.9±30.6	28.5±42.9	0.58
REM sleep onset latency, mean±SD	140.5±92.6	166.0±116.0	0.59
N1 Sleep (%TST), mean±SD	19.9±10.7	18.6±10.9	0.58
N2 Sleep (%TST), mean±SD	46.1±11.7	49.0±13.6	0.35
N3 Sleep (%TST), mean±SD	22.3±12.6	21.6±13.6	0.69
REM Sleep (%TST), mean±SD	11.7±8.7	10.8±9.2	0.56
Arousal index (events/h), mean±SD	25.6±11.9	24.9±11.7	0.75
RDI (events/h), mean±SD	13.2±14.0	13.3±13.8	0.95
AHI in NREM sleep (events/h), mean±SD	11.2±14.0	13.0±14.9	0.78
AHI in REM sleep (events/h), mean±SD	12.3±13.5	14.2±20.5	0.84
PLM index (events/h), mean±SD	33.1±64.8	4.8±11.9	0.33

RLS: restless legs syndrome; RBD: REM Sleep Behavior Disorder; PD: Parkinson disease; SD: standard deviation; WAFA: wake time after final arousal; WASO: wake time after sleep onset; RDI: Respiratory Disturbance Index; AHI: Apnea-Hypopnea Index; PLM: periodic leg movements.

was also observed between IRLSRS and PDQ-39 (r=0.45; p=0.03).

RLS patients had a higher prevalence of chronic insomnia (80%) than those patients without RLS (46%; p=0.004). RLS individuals also had a higher proportion of anosmia and constipation symptoms than the ones without RLS (Table 1). No difference was observed between the polysomnographic values of the groups (Table 2).

Multivariate analysis

For the logistic regression analysis, we have included the variables with p<0.1 (sex, total UPDRS, levodopa equivalent dose, PSQI, PDQ-39, insomnia, anxiety disorder, dyskinesia, motor fluctuation, smell loss, and constipation). After initial analysis with the independent variables, those with higher p values were progressively withdrawn and only those with p<0.05 remained. Thus, the following independent variables were significant in the final model: PSQI (estimated coefficient=0.18; p=0.03), PDQ-39 (estimated coefficient=0.05; p=0.01), and smell loss (estimated coefficient=1.85; p=0.001). The final formula of the logistic regression model was: presence of RLS= -6.06+(PSQI×0.18)+(PDQ-39×0.05)+(smell loss×1.85).

DISCUSSION

Several clinical conditions in PD patients could mimic symptoms of RLS, such as motor fluctuation, cramps, akathisia, and pain related to PD. These factors may confuse the diagnosis to less experienced physicians. RLS diagnosis needs a careful evaluation to ward off these RLS mimics.

As far as we know, no previous paper evaluated the association between anosmia, constipation, and RLS in PD patients. A previous study by Adler et al. compared the olfactory function of RLS individuals with PD subjects. Such study documented normal olfactory functions in the RLS group and deficient olfactory function in the PD group[26], but the study did not evaluate the olfactory function in those individuals with both PD and RLS. A possible explanation for these findings in our study is a higher deposition of alpha-synuclein in PD individuals with RLS compared with the ones without it. We have not made standardized olfactory tests in this study, so the presence of anosmia was only verified by questioning the patient, which is the weakness of this paper.

Constipation is a frequent symptom in PD patients, like anosmia, especially because these are symptoms that, in many cases, precede the onset of motor symptoms[27]. They could be explained by deposition of Lewy bodies in the peripheral autonomic nervous system of PD patients, leading to subsequent sympathetic denervation of the colon[28]. Shneyder et al. showed a higher proportion of constipation and other autonomic complaints in RLS individuals compared to the control group[29]. A possible explanation would be that dopaminergic hypofunction, especially of A11 cells,

would lead to lower stimulation in pre-ganglionic sympathetic neurons, allowing a greater sympathetic flow to the peripheral neurons[30]. Constipation was diagnosed through the patient's complaint. However, no specific criteria were used, which is a negative aspect of this study.

As in several previous studies in PD patients, we did not observe a difference between ages[12,13,18,22,31,32,33]. This characteristic is different from what occurs in the general population, in whom a greater frequency of RLS is observed, as individuals are older, with a peak prevalence between 61 and 70 years[7,8,34,35,36]. A possible explanation for these different data was a higher concentration of individuals over 50 years-old in PD population than in the general population.

No difference between periodic leg movements (PLM) in PD groups with or without RLS was observed, which is not in agreement with data from Nomura et al.[17]. The diversity of doses, schedules, and pharmacokinetics of dopaminergic agonists used in PD individuals could modify the prevalence and intensity of PLM in this group of individuals and explain the large variability of PLM index in PD individuals with RLS.

The present study had some limitations, such as: conduction in a high-complexity outpatient hospital, therefore involving patients with greater severity and duration of the disease, which restricts the possibility of generalization of our data; absence of standardized olfactory tests and specific diagnostic criteria for constipation in this study; absence of dose of serum iron and ferritin levels; low number of patients included, considering a large number of variables analyzed; absence of a control group without PD, reducing the possibility of comparisons; and the cross-sectional design of the study, making it difficult to establish cause-and-effect associations.

Finally, it is noteworthy that RLS is a relevant disease in PD patients. It is also associated with specific characteristics of PD patients, such as smell loss. New controlled studies with larger numbers of PD patients could answer some controversial topics. Furthermore, in the clinical care of PD patients, a systematic and comprehensive assessment of RLS pathology is of mandatory importance.

ACKNOWLEDGMENTS

We are grateful to the patients with PD, whose collaboration was essential to the success of this study

References

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 2nd ed. Westchester (Illinois): AASM; 2005.
2. Walters AS, Hickey K, Maltzman J, Verrico T, Joseph D, Hening W, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology. 1996 Jan;46(1):92-5. https://doi.org/10.1212/wnl.46.1.92
3. Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep. 2000 Aug;23(5):597-602. https://doi.org/10.1093/sleep/23.5.1b
4. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003 Mar;4(2):101-19. https://doi.org/10.1016/s1389-9457(03)00010-8
5. Nichols DA, Allen RP, Grauke JH, Brown JB, Rice ML, Hyde PR, et al. Restless legs syndrome symptoms in primary care: a prevalence study. Arch Intern Med. 2003 Oct;163(19):2323-9. https://doi.org/10.1001/archinte.163.19.2323
6. Tison F, Crochard A, Leger D, Bouee S, Lainey E, El Hasnaoui A. Epidemiology of restless legs syndrome in French adults: a nationwide survey: the INSTANT Study. Neurology. 2005 Jul;65(2):239-46. https://doi.org/10.1212/01.wnl.0000168910.48309.4a
7. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005 Jun;165(11):1286-92. https://doi.org/10.1001/archinte.165.11.1286
8. Eckeli AL, Gitai LL, Dach F, Ceretta H, Sander HH, Passos AD, et al. Prevalence of restless legs syndrome in the rural town of Cassia dos Coqueiros in Brazil. Sleep Med. 2011 Sep;12(8):762-7. https://doi.org/10.1016/j.sleep.2011.01.018
9. Sobreira-Neto MA, Pena-Pereira MA, Sobreira EST, Chagas MHN, Fernandes RMF, Tumas V, et al. High Frequency of Sleep Disorders in Parkinson's Disease and Its Relationship with Quality of Life. Eur Neurol. 2017 Oct;78(5-6):330-7. https://doi.org/10.1159/000481939
10. Braga-Neto P, da Silva-Junior FP, Sueli Monte F, de Bruin PF, de Bruin VM. Snoring and excessive daytime sleepiness in Parkinson's disease. J Neurol Sci. 2004 Jan;217(1):41-5. https://doi.org/10.1016/j.jns.2003.08.010
11. Comella CL. Sleep disorders in Parkinson's disease: an overview. Mov Disord. 2007 Sep;22 Suppl 17:S367-73. https://doi.org/10.1002/mds.21682
12. Guerreiro TM, Nishikawa DR, Ferreira LC, Melo HA, Prado RC. Restless legs syndrome in Parkinson's disease: clinical characteristics and biochemical correlations. Arq Neuropsiquiatr. 2010 Dec;68(6):869-72. https://doi.org/10.1590/s0004-282x2010000600007
13. Verbaan D, van Rooden SM, van Hilten JJ, Rijsman RM. Prevalence and clinical profile of restless legs syndrome in Parkinson's disease. Mov Disord. 2010 Oct;25(13):2142-7. https://doi.org/10.1002/mds.23241
14. Rijsman RM, Schoolderman LF, Rundervoort RS, Louter M. Restless legs syndrome in Parkinson's disease. Parkinsonism Relat Disord. 2014 Jan;20 Suppl 1:S5-9. https://doi.org/10.1016/s1353-8020(13)70004-x
15. Clemens S, Hochman S. Conversion of the modulatory actions of dopamine on spinal reflexes from depression to facilitation in D3 receptor knock-out mice. J Neurosci. 2004 Dec;24(50):11337-45. https://doi.org/10.1523/jneurosci.3698-04.2004
16. Dauvilliers Y, Winkelmann J. Restless legs syndrome: update on pathogenesis. Curr Opin Pulm Med. 2014 Nov;19(6):594-600. https://doi.org/10.1097/mcp.0b013e328365ab07
17. Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K. Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord. 2006 Mar;21(3):380-4. https://doi.org/10.1002/mds.20734

18. Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. Arch Neurol. 2002 Mar;59(3):421-4. https://doi.org/10.1001/archneur.59.3.421

19. Nomura T, Inoue Y, Nakashima K. Clinical characteristics of Restless legs syndrome in patients with Parkinson's disease. J Neurol Sci. 2006 Dec;250(1-2):39-44. https://doi.org/10.1016/j.jns.2006.06.023

20. Loo HV, Tan EK. Case-control study of restless legs syndrome and quality of sleep in Parkinson's disease. J Neurol Sci. 2008 Mar;266(1-2):145-9. https://doi.org/10.1016/j.jns.2007.09.033

21. Krishnan PR, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: a case-controlled study. Mov Disord. 2003 Feb;18(2):181-5. https://doi.org/10.1002/mds.10307

22. 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 Mar;24(4):579-82. https://doi.org/10.1002/mds.22410

23. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Westchester (Illinois): AASM; 2013.

24. Del-Ben C, Vilela J, Crippa J, Hallak J, Labate C, Zuardi A. Reliability of the structured clinical interview for DSM-IV - Clinical version (SCID-CV) translated into Portuguese. Rev Bras Psiquiatr. 2001 Set;23(3):156-9. https://dx.doi.org/10.1590/S1516-44462001000300008

25. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM Manual for Scoring of Sleep and Associated Events. 1st ed. Westchester (Illinois): AASM; 2007.

26. Adler CH, Gwinn KA, Newman S. Olfactory function in restless legs syndrome. Mov Disord. 1998 May;13(3):563-5. https://doi.org/10.1002/mds.870130332

27. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol. 2008 Apr;15 Suppl 1:14-20. https://doi.org/10.1111/j.1468-1331.2008.02056.x

28. Edwards LL, Quigley EM, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease: frequency and pathophysiology. Neurology. 1992 Apr;42(4):726-32. https://doi.org/10.1212/wnl.42.4.726

29. Shneyder N, Adler CH, Hentz JG, Shill H, Caviness JN, Sabbagh MN, et al. Autonomic complaints in patients with restless legs syndrome. Sleep Med. 2013 Dec;14(12):1413-6. https://doi.org/10.1016/j.sleep.2013.08.781

30. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009 May;32(5):589-97. https://doi.org/10.1093/sleep/32.5.589

31. Bhalsing K, Suresh K, Muthane UB, Pal PK. Prevalence and profile of Restless Legs Syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. Parkinsonism Relat Disor. 2013 Apr;19(4):426-30. https://doi.org/10.1016/j.parkreldis.2012.12.005

32. 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 Nov;310(1-2):286-8. https://doi.org/10.1016/j.jns.2011.08.012

33. Gomez-Esteban JC, Zarranz JJ, Tijero B, Velasco F, Barcena J, Rouco I, et al. Restless legs syndrome in Parkinson's disease. Mov Disord. 2007 Oct;22(13):1912-6. https://doi.org/10.1002/mds.21624

34. Cho YW, Shin WC, Yun CH, Hong SB, Kim JH, Allen RP, et al. Epidemiology of restless legs syndrome in Korean adults. Sleep. 2008 Feb;31(2):219-23. https://doi.org/10.1093/sleep/31.2.219

35. Sevim S, Dogu O, Camdeviren H, Bugdayci R, Sasmaz T, Kaleagasi H, et al. Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. Neurology. 2003 Dec;61(11):1562-9. https://doi.org/10.1212/01.wnl.0000096173.91554.b7

36. Taşdemir M, Erdoğan H, Börü UT, Dilaver E, Kumaş A. Epidemiology of restless legs syndrome in Turkish adults on the western Black Sea coast of Turkey: A door-to-door study in a rural area. Sleep Med. 2010 Jan;11(1):82-6. https://doi.org/10.1016/j.sleep.2008.10.008