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ARTICLE

Restless legs syndrome in Parkinson's disease and increased cardiovascular risk

Síndrome das pernas inquietas em doença de Parkinson e aumento do risco cardiovascular

Maren de Moraes e Silva[1], Cezar Henrique Lorenzi[2], Blenda Barreto Schneider[3], Catherine Enk Fischer Seidel[4], Isabela Salomé[5], Viktor Cleto Morais Gianini[6], Renata Ramina Pessoa[1], Pilar Bueno Siqueira Mercer[1], Maria Carolina Zavagna Witt[1]

ABSTRACT

Restless legs syndrome (RLS) is a disorder commonly found in patients with Parkinson's disease, with descriptions for both conditions impairing dopaminergic transmission in central nervous system. Previous studies in varied populations indicate an association between the presence of RLS and increased cardiovascular risk and, so far, there are no consistent studies of this association in Parkinson's disease. **Objective:** To analyze the influence of RLS on cardiovascular risk in patients with Parkinson's disease. **Methods:** We reviewed the medical records of 202 patients diagnosed with Parkinson's disease and verified the presence of RLS, cardiovascular comorbidities, blood pressure measurements, lipid profiles and Framingham Risk Scores. **Results:** Statistically significant higher values of total cholesterol were found for the RLS group (mean 216.6 mg/dL), as well as for LDL cholesterol (mean 145 mg/dL). No statistical difference was found among the other factors. **Conclusion:** Patients with Parkinson's disease and RLS have a higher prevalence of dyslipidemia than patients without RLS, suggesting a correlation between restless legs and hyperlipidemia. It is questioned whether the dopaminergic substrate is the main factor in the genesis of the syndrome, as even with the use of dopaminergic agonists by both groups, it was possible to observe differences between groups. The hypothesis of the real interference of the syndrome treatment as a protective factor for cardiovascular risk was generated.

Keywords: Parkinson disease; restless legs syndrome; cardiovascular diseases; dyslipidemias.

RESUMO

Síndrome das pernas inquietas é um distúrbio comumente encontrado em pacientes com doença de Parkinson (DP), havendo descrições para ambas as condições de prejuízos na transmissão dopaminérgica no sistema nervoso central. Estudos prévios em populações diversas indicam associação entre a presença da síndrome e aumento do risco cardiovascular, não havendo, até o momento, pesquisas consistentes a respeito desta associação em DP. **Objetivo:** Analisar a influência da síndrome das pernas inquietas no risco cardiovascular em pacientes com DP. **Métodos:** Foram revisados prontuários de 202 pacientes com diagnóstico de DP e verificada a presença de síndrome das pernas inquietas, comorbidades cardiovasculares, aferições de pressão arterial, lipidograma e escore de Framingham. **Resultados:** Valores maiores e estatisticamente significativos de colesterol total foram encontrados para o grupo com pernas inquietas (média de 216.6 mg/dL), assim como para colesterol LDL (média de 145 mg/dL). Não foi encontrada diferença estatística entre os demais fatores. **Conclusões:** Pacientes com DP e síndrome das pernas inquietas têm maior prevalência de dislipidemia do que pacientes sem a síndrome, o que sugere correlação entre síndrome das pernas inquietas e hiperlipidemia. É posto em prova o substrato dopaminérgico como principal na gênese da síndrome, uma vez que, mesmo sob o uso de agonistas dopaminérgicos por ambos os grupos, foi possível observar diferenças entre os estratos. Gerada a hipótese da real interferência do tratamento da síndrome como fator de proteção para o risco cardiovascular.

Palavras-chave: Doença de Parkinson; síndrome das pernas inquietas; doenças cardiovasculares; dislipidemias.

Restless legs syndrome (RLS) is a disorder characterized by an uncontrollable need to move the legs, that occurs during rest, and which is relieved by movement of the lower limbs[1]; however, the sensation may occur in other parts of the body as well. In this way, RLS interferes markedly with the individuals sleep quality. In its pathophysiology, there is

[1]Hospital da Cruz Vermelha Brasileira Filial do Paraná, Departamento de Neurologia, Curitiba PR, Brasil;
[2]Universidade Federal do Paraná,Curitiba PR, Brasil;
[3]Universidade Positivo, Curitiba PR, Brasil;
[4]Faculdade Evangélica do Paraná, Curitiba PR, Brasil;
[5]Pontifícia Universidade Católica do Paraná, Curitiba PR, Brasil;
[6]Faculdades Pequeno Príncipe, Curitiba PR, Brasil.
Correspondence: Maren de Moraes e Silva; Avenida Vicente Machado, 1310; 80420-011Curitiba PR, Brasil; E-mail: marenms@live.com
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a decrease in central nervous system dopaminergic levels, especially at night[2,3], with dopaminergic agonists playing a role in improving symptoms. Other theories, such as iron accumulation, have also been cited in literature[3].

In previous studies involving diverse populations, RLS seems to increase several cardiovascular risk factors[4,5,6], mainly due to interference in sleep-wake cycle, culminating in an exacerbated sympathetic activity in this period[4,5,6,7,8]. There is also evidence that RLS can lead to impairment in cardiovascular system autonomic control, regardless the presence of changes in sleep quality or periodic leg movements[9].

Both RLS and Parkinson's disease (PD) present with alterations in dopaminergic transmission in their pathophysiology. In addition, studies have shown that the prevalence of RLS in patients with PD is higher than in general population[10,11,12]. Taking into account the possible deleterious effect of RLS on cardiovascular function, it is essential that the associations between these morbidities be established, given the frequency of the syndrome in this population. The present study sought to establish the prognostic impact of RLS in Parkinson's disease.

METHODS

This study was initiated after approval by the research ethics committee of Universidade Positivo under the registration number CAAE 73905517.3.0000.0093 and conducted according to ethical standards in accordance with Resolution 466/2012.

Participants

The records of patients diagnosed with idiopathic PD who attend a specialized center in a city in southern Brazil were reviewed. We included patients diagnosed with PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[13]. Only patients with 50 years or older were included in the study. Alcohol abuse patients, smokers, patients who had diagnosed coronary artery disease before onset of RLS or who presented with a weight gain of more than 5 kg in the last six months were excluded from the study.

Data selection

A retrospective observational study was performed. The patients were previously selected through medical records analysis, according to the inclusion and exclusion criteria. The patients were divided into two groups: PD+RLS patients and PD patients without the syndrome (controls). The diagnosis of RLS was made according to the diagnostic criteria of American Academy of Sleep Medicine[2].

Cardiovascular risk was evaluated using the Framingham Risk Score, a previous vascular event, blood pressure measurement, laboratory examination and presence of peripheral arterial disease.

Data analysis

Continuous data were expressed as means. Frequencies were expressed in percentages. Numerical variables were compared using the ANOVA test, while categorical variables were analyzed using the chi-square test. Statistical significance was set at $p < 0.05$.

RESULTS

Population characteristics

Data were analyzed for 202 patients in total: 57.43% were male and the population mean age was 70.12 ± 9.49 years. The mean age at onset of PD symptoms was 59.86 ± 10.64 years, with a mean duration of symptoms of 9.64 ± 5.68 years at the time of our evaluation. The prevalence of RLS was 7.92% (16 patients). The sample distribution in relation to demographics and comorbidities for PD + RLS and control groups is shown in Table 1.

Cardiovascular risk and relations

The occurrence of stroke, acute myocardial infarction and heart failure after the diagnosis of RLS was verified, although there was no prevalence of these morbidities in the PD+RLS group. In the control group, the occurrence of these conditions was 7.43%, 2.47% and 1.98%, respectively.

The Framingham Risk Score was calculated for participating patients, with a mean score of 15.27 ± 7.76 for control group and 12.90±4.53 for PD+RLS group. However, the

Table 1. Characteristics and comorbidities distribution by group.

Variable	PD+RLS group (n = 16)	Control group (n = 186)	p-value
Male %	43.75	58.60	0.249
Mean age (years) ± SD	67.75 ± 12.94	70.33 ± 9.07	0.183
Mean disease duration (years) ± SD	10.50 ± 7.28	9.57 ± 12.35	0.787
PD mean age at onset (years) ± SD	56.87 ± 11.17	60.44 ± 10.52	0.121
Hypertension %	50.00	47.85	0.976
Peripheral arterial disease %	0	2.15	-
Diabetes %	18.75	17.74	0.919

PD: Parkinson's disease; RLS: restless legs syndrome; SD: standard deviation

Table 2. Lipid profile by group.

Variable	PD + RLS group	Control group	p-value
mean TC (mg/dL) ± SD	216.60 ± 49.73	176 ± 35.34	0.021
mean HDL (mg/dL)) ± SD	41.68 ± 6.71	49.17 ± 15.69	0.292
mean LDL (mg/dL)) ± SD	145 ± 39.35	94 ± 37.20	0.007

PD: Parkinson's disease; RLS: restless legs syndrome; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation.

difference found between groups wasn't statistically significant (p = 0.605).

Regarding systolic blood pressure, a mean of 121.43±30.23 mmHg (median 120) was observed for control group and 121.20 ± 18.23 mmHg (median 120) for PD+RLS group. This difference wasn't statistically significant (p = 0.976).

Participants lipid profile of was also evaluated, with a mean in general population of 179.50 ± 38.02 mg/dL for total cholesterol. The separate groups analysis is shown in Table 2. Among control group, 19.35% of patients had a diagnosis of dyslipidemia and had received statin prescriptions in previous consultations, compared with 43.75% of the PD+RLS group.

DISCUSSION

It's believed that subcortical dopaminergic dysfunctions play an important role in RLS genesis, as well as in PD, with dopaminergic agonists responsible for symptoms improvement in both conditions[3]. In addition, a risk relation can be established between RLS and PD[14], with a greater occurrence of the syndrome in patients with PD[10,11,12]. Impairment in dopaminergic transmission, common in the etiology of PD and RLS, may explain why the prevalence of RLS in patients with PD is high.

The relation between RLS and cardiovascular risk has previously been explored, but at present, there is no confirmation of this relation in PD population, specifically. It's postulated that RLS can lead to heart disease through several potential mechanisms: its negative effect on sleep quality and duration, coexisting sympathetic activation accompanying periodic limb movements during sleep, or presence of common risk factors for heart disease[8]. In addition, interruption of sleep, common in patients with RLS, increases the daytime heart rate and blood pressure through elevated peripheral sympathetic tonus[5,15]. The present study, however, didn't directly assess the impact of this morbidity on sleep quality.

In our study, RLS prevalence was compatible with previous literature findings for general population, ranging from 5% to 10%[16,17,18,19] and involving more women than men. The difference between genders may be due to the fact that women generally perceive and report symptoms more often than men and because of hormonal differences. In previous studies addressing RLS in PD exclusively, showed prevalence rates with great variability (0% to 50%)[11,12,20,21]. However, due to the fact that the treatment of PD involves dopaminergic compounds, which also alleviate RLS symptoms[17], the true prevalence of RLS maybe masked in this population[22]. This risk, however, is called into question by studies that have reported an increased prevalence of RLS, compared with general population, in patients with long-term dopamine use, indicating the possible contradictory correlation of RLS increasing with the duration of previous dopaminergic drug treatment[23,24]. Because the present study showed a statistically significant difference for lipid profile changes, it's important to reconsider the role of dopamine as unique in genesis of this syndrome, taking into account the probability of other questions related to the possible increase in cardiovascular risk of these patients, such as common risk factors. Moreover, in our study, no statistically significant difference was found regarding the length of PD treatment and presence of RLS.

Regarding cardiovascular risk, we analyzed the Framingham Risk Score, blood pressure measurements and lipid profiles, and found a statistically significant relation only for high values of total cholesterol and LDL (low density lipoprotein), which appeared to be higher in PD patients with RLS. We could find no data in literature comparing RLS and lipid profiles in PD population. There is already evidence that the prevalence of dyslipidemia is higher in individuals with RLS than in individuals without the syndrome[25,26]. A prospective study found that elevated levels of total cholesterol were associated with a higher risk of developing RLS, which didn't change significantly after exclusion of patients using statins, indicating that the correlation didn't occur due to drug side effects[27]. There was also a correlation between sleep quality in patients with RLS and dyslipidemia, with an association between poorer sleep quality and LDL levels, shorter sleep duration and total cholesterol levels, and greater daytime dysfunction and LDL levels in patients with RLS[28]. Metabolic disorders may occur along with activation of the hypothalamic-pituitary-adrenal axis and with inflammation, which may trigger a role in RLS genesis[29]. In addition, there are reports of RLS caused by microembolization of cholesterol crystals[30]. These data corroborate this study findings, indicating a correlation between dyslipidemia and RLS; however, the findings described here are new as they are specific for the PD population.

Regarding the relation between cardiovascular risk factors and RLS in other morbidities, we found conflicting evidence. A prospective study in United Kingdom revealed an association between RLS and incidence of stroke, but an

association wasn't found between RLS and ischemic heart disease[31]. This finding was corroborated by another paper, in which it was also observed that the syndrome was more frequent in individuals with various comorbidities, including high body mass index, hypertension and diabetes[32]. Contrary to this analysis, some studies have shown that RLS is associated with cardiovascular disease in patients with frequent symptoms and RLS diagnosed for more than three years[8,33]. Li et al.[8] identified a significant association between long-term RLS and coronary disease. According to their study, women with RLS for more than three years were at increased risk for coronary heart disease, an association that was independent of the main risk factors for coronary disease. Other studies have suggested a lower cardiac vagal modulation and lower heart rate response to orthostatic stress in subjects with RLS[34,35]. The positive correlation between RLS and cardiovascular risk obtained by these studies maybe explained by the reduction of cardiovascular baroreflex gain and greater peripheral vascular resistance observed in patients with RLS - factors not attributed to differences in sleep quality, suggesting that the syndrome can directly contribute to changes in cardiovascular system autonomic control [9]. Corroborating the above findings, another study indicated that RLS may be related to cardiovascular disease, coronary disease and hypertension, but with different relative risks according to primary or secondary classification of RLS. Primary RLS would be a risk factor for hypertension, but not for cardiovascular disease or coronary disease. However, when secondary to another morbidity, including PD, RLS would be associated with the three conditions: hypertension, cardiovascular disease and coronary disease[36].

A previous study by Oh et al.[31] failed to find a statistically significant association between PD, RLS and cardiovascular diseases; however, according to a study by Banno et al.[25], nocturnal hypertension and supine hypertension occurred more frequently in patients with PD and RLS than in patients with PD without RLS. In the present study, there were no significant differences in blood pressure values between the control group and the PD+RLS group, while other cardiovascular comorbidities were not frequent enough for an adequate comparison.

This article is limited by being retrospective, and the sample analyzed was relatively small, which may justify not identifying the correlation of RLS with other factors, such as a statistically significant difference for the Framingham Risk Score or blood pressure, already described in previous studies with various populations. Regarding the overlap between PD and RLS treatment as a possible factor for diagnostic masking, our results test the dopaminergic substrate as the main factor in the RLS genesis, as even with the use of dopaminergic agonists in both groups, PD+RLS and control, it was possible to observe differences between the strata, a theory corroborated by previous findings[3,24]. A hypothesis is generated, as well, of the real interference of the treatment of RLS syndrome as a protection factor for cardiovascular risk.

Our findings, which indicated a relationship between an unfavorable lipid profile of patients with PD (high total cholesterol and LDL) and the presence of RLS, are new and not previously reported in the literature, but consistent with findings in other populations. Future research is needed to confirm this possible relationship. Based on this, it's possible that new forms of primary prevention and overall care may be found for patients with PD.

References

1. American Academy of Sleep Medicine (AASM). The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Wenchester): American Academy of Sleep Medicine; 2005.
2. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology. 2006 Jul;67(1):125-30. https://doi.org/10.1212/01.wnl.0000223316.53428.c9
3. Winkelman JW. Considering the causes of RLS. Eur J Neurol. 2006 Oct;13 Suppl 3:8-14.
4. Billars L, Hicks A, Bliwise D, Sigmundsson T. Hypertension risk and PLMS in restless legs syndrome. Sleep. 2007;30:A297-8.
5. Ekstedt M, Akerstedt T, Söderström M. Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. Psychosom Med. 2004 Nov-Dec;66(6):925-31. https://doi.org/10.1097/01.psy.0000145821.25453.f7
6. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007 Apr;68(15):1213-8. https://doi.org/10.1212/01.wnl.0000259036.89411.52
7. Manconi M, Ferri R, Zucconi M, Clemens S, Rundo F, Oldani A et al. Effects of acute dopamine-agonist treatment in restless legs syndrome on heart rate variability during sleep. Sleep Med. 2011 Jan;12(1):47-55.
8. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. Circulation. 2012 Oct;126(14):1689-94. https://doi.org/10.1161/CIRCULATIONAHA.112.112698
9. Bertisch SM, Muresan C, Schoerning L, Winkelman JW, Taylor JA. Impact of Restless Legs Syndrome on Cardiovascular Autonomic Control. Sleep (Basel). 2016 Mar;39(3):565-71. https://doi.org/10.5665/sleep.5528
10. Guerreiro TM, Nishikawa DR, Ferreira LC, Melo HA, Prado RC. Restless legs syndrome in Parkinson's disease: clinical characteristics and biochemical correlations. ArqNeuropsiquiatr. 2010 Dec;68(6):869-72. https://doi.org/10.1590/S0004-282X2010000600007
11. Braga-Neto P, Silva-Júnior FP, Sueli Monte F, Bruin PF, 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
12. 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
13. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J NeurolNeurosurgPsychiatry. 1992 Mar;55(3):181-4. https://doi.org/10.1136/jnnp.55.3.181

14. Grupo Brasileiro de Estudos em Síndrome das Pernas Inquietas - GBE-SPI. [Restless legs syndrome: diagnosis and treatment. Opinion of Brazilian experts]. ArqNeuropsiquiatr. 2007;65 3a:721-7. Portuguese. https://doi.org/10.1590/S0004-282X2007000400035

15. Davies RJ, Belt PJ, Roberts SJ, Ali NJ, Stradling JR. Arterial blood pressure responses to graded transient arousal from sleep in normal humans. J Appl Physiol (1985). 1993 Mar;74(3):1123-30. https://doi.org/10.1152/jappl.1993.74.3.1123

16. 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

17. 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

18. Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. Chest. 2006 Jan;129(1):76-80. https://doi.org/10.1378/chest.129.1.76

19. Vogl FD, Pichler I, Adel S, Pinggera GK, Bracco S, De Grandi A et al. Restless legs syndrome: epidemiological and clinicogenetic study in a South Tyrolean population isolate. Mov Disord. 2006 Aug;21(8):1189-95. https://doi.org/10.1002/mds.20922

20. Lang AE, Johnson K. Akathisia in idiopathic Parkinson's disease. Neurology. 1987 Mar;37(3):477-81. https://doi.org/10.1212/WNL.37.3.477

21. Tan EK, Lum SY, Wong MC. Restless legs syndrome in Parkinson's disease. J Neurol Sci. 2002 Apr;196(1-2):33-6. https://doi.org/10.1016/S0022-510X(02)00020-5

22. 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 RelatDisord. 2013 Apr;19(4):426-30. https://doi.org/10.1016/j.parkreldis.2012.12.005

23. 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

24. 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

25. Banno K, Delaive K, Walld R, Kryger MH. Restless legs syndrome in 218 patients: associated disorders. Sleep Med. 2000 Jul;1(3):221-9. https://doi.org/10.1016/S1389-9457(00)00023-X

26. Schlesinger I, Erikh I, Avizohar O, Sprecher E, Yarnitsky D. Cardiovascular risk factors in restless legs syndrome. Mov Disord. 2009 Aug;24(11):1587-92. https://doi.org/10.1002/mds.22486

27. De Vito K, Li Y, Batool-Anwar S, Ning Y, Han J, Gao X. Prospective study of obesity, hypertension, high cholesterol, and risk of restless legs syndrome. Mov Disord. 2014 Jul;29(8):1044-52. https://doi.org/10.1002/mds.25860

28. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology. 2008 Jan;70(1):35-42. https://doi.org/10.1212/01.wnl.0000287072.93277.c9

29. Schilling C, Schredl M, Strobl P, Deuschle M. Restless legs syndrome: evidence for nocturnal hypothalamic-pituitary-adrenal system activation. MovDisord. 2010 Jun;25(8):1047-52. https://doi.org/10.1002/mds.23026

30. Harvey JC. Cholesterol crystal microembolization: a cause of the restless leg syndrome. South Med J. 1976 Mar;69(3):269-72. https://doi.org/10.1097/00007611-197603000-00007

31. Oh YS, Kim JS, Park IS, Song IU, Son YM, Park JW et al. Association between nocturnal/supine hypertension and restless legs syndrome in patients with Parkinson's disease. J Neurol Sci. 2014 Sep;344(1-2):186-9. https://doi.org/10.1016/j.jns.2014.06.056

32. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med. 2006 Oct;7(7):545-52. https://doi.org/10.1016/j.sleep.2006.01.004

33. Cikrikcioglu MA, Hursitoglu M, Erkal H, Kınas BE, Sztajzel J, Cakirca M et al. Oxidative stress and autonomic nervous system functions in restless legs syndrome. Eur J Clin Invest. 2011 Jul;41(7):734-42. https://doi.org/10.1111/j.1365-2362.2010.02461.x

34. Izzi F, Placidi F, Romigi A, Lauretti B, Marfia GA, Mercuri NB et al. Is autonomic nervous system involved in restless legs syndrome during wakefulness? Sleep Med. 2014 Nov;15(11):1392-7. https://doi.org/10.1016/j.sleep.2014.06.022

35. Van Den Eeden SK, Albers KB, Davidson JE, Kushida CA, Leimpeter AD, Nelson LM et al. Risk of Cardiovascular Disease Associated with a Restless Legs Syndrome Diagnosis in a Retrospective Cohort Study from Kaiser Permanente Northern California. Sleep (Basel). 2015 Jul;38(7):1009-15. https://doi.org/10.5665/sleep.4800

36. Fereshtehnejad SM, Shafieesabet M, Shahidi GA, Delbari A, Lökk J. Restless legs syndrome in patients with Parkinson's disease: a comparative study on prevalence, clinical characteristics, quality of life and nutritional status. Acta Neurol Scand. 2015 Apr;131(4):211-8. https://doi.org/10.1111/ane.1230