Title: Restless legs syndrome in Multiple Sclerosis patients: a contributing factor for fatigue, impaired functional capacity, and diminished health-related quality of life

Author(s): Giannaki, Christoforos D., Aristotelous, Panagiotis, Stefanakis, Manos, Hadjigeorgiou, Georgios M., Manconi, Mauro, Leonidou, Eleni, Sakkas, Giorgos K. and Pantzaris, Marios

DOI: https://doi.org/10.1080/01616412.2018.1454719

Reference: Giannaki, Christoforos D., Aristotelous, Panagiotis, Stefanakis, Manos, Hadjigeorgiou, Georgios M., Manconi, Mauro, Leonidou, Eleni, Sakkas, Giorgos K. and Pantzaris, Marios (2018) Restless legs syndrome in Multiple Sclerosis patients: a contributing factor for fatigue, impaired functional capacity, and diminished health-related quality of life. Neurological Research. pp. 1-7. ISSN 0161-6412

Title Page

Title: Restless legs syndrome in Multiple Sclerosis patients: a contributing factor for fatigue, impaired functional capacity and diminished health-related quality of life.

Authors: Christoforos D. Giannaki[a,b], Panagiotis Aristotelous[a], Manos Stefanakis[a], Georgios M. Hadjigeorgiou[c], Mauro Manconi[d], Eleni Leonidou[b], Giorgos K. Sakkas[e], Marios Pantzaris[b]

Affiliations: [a]Department of Life and Health Sciences, University of Nicosia, Nicosia, Cyprus; [b]The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus; [c]Department of Medicine, University of Thessaly, Greece; [d]Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital (EOC) of Lugano, Lugano, and Neurology Department Inselspital, Bern University Hospital, Switzerland; [e]Faculty of Sport and Health Sciences, University of St Mark & St John, Plymouth, UK

Corresponding Author: Christoforos D. Giannaki, PhD
Department of Life and Health Sciences
University of Nicosia, Nicosia, Cyprus
46 Makedonitisas Avenue, CY 1700
Tel: +357-22842325; Fax: +357-22842399
ORCID ID: 0000-0003-0029-1189
E-mail: giannaki.c@unic.ac.cy

Author Details:

Panagiotis Aristotelous: Department of Life and Health Sciences, University of Nicosia, 46 Makedonitissas Ave, CY1700, Nicosia, Cyprus.

Email: Panayiotis.aristotelous@gmail.com; Tel: +357-22842325

Manos Stefanakis: Department of Life and Health Sciences, University of Nicosia, 46 Makedonitissas Ave, CY1700, Nicosia, Cyprus.

Email: stefanakis.m@unic.ac.cy; Tel: +357-22842564

Georgios M. Hadjigeorgiou: Department of Medicine, University of Thessaly, Mezourlo, 41110, Larissa, Greece

Email: gmhadji@med.uth.gr ;Tel: +30 2413502790

Mauro Manconi: Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital (EOC) of Lugano, Via Tesserete 46, 6903, Lugano, Switzerland

Email: Mauro.Manconi@eoc.ch ;Tel: +41 91 811 6825

Eleni Leonidou: The Cyprus Institute of Neurology and Genetics, 6 International Airport Ave., CY1683, Nicosia, Cyprus

Email: elenil@cing.ac.cy; Tel: +357-22392740

Giorgos K. Sakkas: Faculty of Sport and Health Sciences, University of St Mark & St John, Plymouth, Plymouth, PL6 8BH, United Kingdom

Email: gsakkas@marjon.ac.uk ; Tel: +44(0)1752-636837

Marios Pantzaris: The Cyprus Institute of Neurology and Genetics, 6 International Airport Ave., CY1683, Nicosia, Cyprus

Email: pantzari@cing.ac.cy; Tel: +357-22392740

Acknowledgments: We would like to thank all the patients who volunteered for the purposes of the study as well as Mr. Stelios Shiakallis and Mr. Neophytos Michael for their help and support during the period of this study.

Disclosure of interest: The authors report no conflicts of interest

Word count: 4790

Abstract

Objectives: Restless legs syndrome (RLS) symptoms are common in Multiple Sclerosis (MS) patients. The aim of the current study was to examine for the first time whether RLS could affect the functional capacity and various contributors parameters related to quality of life and fatigue in MS patients.

Methods: According to their RLS status, fifty relapsing-remitting MS patients were divided into the RLS (n= 10) and non-RLS group (n= 40). Specific questionnaires were used in order to assess the health-related quality of life (HRQoL), fatigue levels, sleep quality, daily sleepiness and depression symptoms of the patients. Functional capacity was examined using a battery of functional tests. Total body and visceral fat levels were assessed via bioelectrical impedance analyzers.

Results: Sleep quality, depression, fatigue and HRQoL levels were found to be significantly worse in the patients with RLS compared to their free-RLS counterparts ($p < 0.05$). In addition, the patients with RLS were found to exhibit further impairments in their performance in various functional tests related mainly with strength levels of lower extremities ($p < 0.05$). Finally, the patients with RLS were found to have significantly higher both total and trunk fat levels compared to the patients without RLS ($p < 0.05$). A strong correlation was observed between the severity of RLS symptoms, sleep quality, fatigue and QoL levels.

Discussion: It seems that RLS contributes even further to impairments on sleep quality, fatigue, functional capacity and therefore HRQoL levels in relapsing-remitting MS patients, whilst for first time a link between high fat levels has been revealed also.

Keywords: sleep; functional capacity; depression; body fat

Introduction

Restless legs syndrome (RLS)/Willis-Ekbom disease is a common neurologic disorder characterized by an irresistible need to move the legs, usually accompanied by unpleasant sensations [1], which begins or worsen during inactivity, especially in the evening/night, and improves or disappear by movement [1]. Even though the mechanism behind RLS is unclear, available data suggest a possible dysfunction of dopaminergic, opioid and iron metabolism in the central nervous system [2]. Recently, another interesting theory advocates peripheral hypoxia [3] as an interesting peripheral trigger of RLS symptoms. RLS is more common and more severe in Multiple Sclerosis (MS) [4, 5] than in general population, with a prevalence rate ranging between 13.3% to 65.1% [6].

Sleep disorders merit further attention in patients with MS given the potential impact on overall health and health-related quality of life (HRQoL) [7]. Moreover, sleep disorders can contribute to depression and fatigue, symptoms that are extremely frequent in MS patients[7], resulting to impaired HRQoL [8]. Indeed, evidences revealed that the MS patients with RLS exhibit poorer subjective sleep quality and greater disability and fatigue levels compared to their free-RLS counterparts[9]. It is still unknown whether RLS can affect the functional capacity and body composition of the MS patients, fact that could significantly contribute to even further impairments on HRQoL, fatigue and mental health of the current population.

The aim of the current study was to examine for the first time whether RLS could affect the functional capacity and various contributors parameters related to quality of life and fatigue in relapsing-remitting MS patients. The null hypothesis is that the MS patients suffering also from RLS have the same level of health-related quality of life, functional capacity and fatigue compared to the MS patients without RLS.

Methods

Participants

Fifty patients with relapsing-remitting MS were agreed to participate in this study. MS was diagnosed according to the revised McDonald criteria (2005), whilst the patients' disability level was assessed by the expanded disability status scale (EDSS) [10]. The examination was performed always during a period of disease remission, at least 3 months after the last clinical relapse. The patients need to have an Expanded Disability Status Scale (EDSS) score between 0 and 5.5 and an age of 18-65 years. The patients were consecutively recruited from the neurology clinics of the Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus. According to their RLS status, the patients were divided into two groups: the RLS group (n= 10, MS-RLS+) and the non-RLS group (n=40, MS-RLS-). RLS was diagnosed by a face to face interview conducted by a neurologist expert in RLS by using the updated diagnostic criteria from the International RLS Study Group (IRLSSG) [1], whilst the severity of the RLS symptoms was evaluated using the IRLSSG severity rating scale (IRLS) [11]. All of the patients receive the diagnosis of MS within 2 years before of the RLS assessment. Inclusion criteria were that patients experienced the RLS symptoms at least three times per week, MRI showing lesions consistent with MS and at least one documented clinical relapse. Patients excluded from the study if they have been diagnosed with other neurological diseases (other than MS), have any signs or symptoms of secondary RLS (eg, RLS secondary to chronic renal failure, pregnancy, iron deficiency and anaemia) or any recent clinical relapse (within 3 months prior to the initialization of the study). All patients gave their written consent. The study conformed to the principles enumerated in the Helsinki Declaration and was approved by the local Ethics Committee (national).

Anthropometry and body composition assessment

The patients' height was measured using a standing stadiometer (Seca model 720, Germany). Body weight was recorded to the nearest 0.05 kg using an analogue scale (Seca model 755, Germany). Body mass index (BMI) was calculated as body weight divided by height squared. Total body fat and trunk fat were both assessed by bioelectrical impedance analyzers (Bodystat, Quadscan 4000 and Tanita AB 140 Viscan respectively). The later analyzer provided also abdominal girth data of the patients in cm.

Questionnaires

Health-related quality of life levels were evaluated using the SF-36 questionnaire [12]. The patients' depressive symptoms were assessed by using the Beck Depression Inventory (BDI) [13]. Subjective sleep quality was assessed by using the Pittsburg sleep quality index (PSQI) [14]. Fatigue levels were assessed by using the fatigue severity scale (FSS) [15]. Finally, the patients' daily sleepiness status was assessed by using the Epworth sleepiness scale (ESS) [16]. We should note that all questionnaires were completed using the interview method.

Functional capacity assessment

The patients' functional capacity was assessed by a battery of tests. In particular, the patients performed two Sit-to-Stand tests (STS-5 and STS-60) [17] the six minute walk test [18] and the timed up and go test (TUG) [19]. The STS-5 requires from the patient to perform five sit-to-stand cycles as fast as possible measured in seconds, and can be used as an indicator of the patient's lower extremities strength. The STS-60 is a similar test that requires from the patient to stand up and sit down to a chair as many times as possible in 60 seconds. The score is the total number of sit to stands cycles within 60 seconds (the number achieved in 30 seconds was recorded also) and it is an index of muscular endurance. The six minute walk test requires from the patient to cover as much ground is possible in six minutes (the covered distance was recorded in meters). The TUG test requires from the patient to rise from a chair, walk to a line on the floor three meters away, turn and walk back to the chair and sit down again. A faster time indicates a better functional performance.

Biochemical Assessment

The biochemical examination of blood samples including haemoglobin, hematocrit, iron, and ferritin was performed at the clinical lab of the Cyprus Institute of Neurology and Genetics under standard hospital procedures

Statistical Analysis

The normality of data was assessed by the Kolmogorov–Smirnov test. Unpaired *t*-tests were used to compare the two groups for continuous normally distributed variables, Mann-Whitney *U* test was used for non-normally distributed variables, whilst chi-square test was used for categorical variables. The Pearson correlation test was used to assess the relationship between the severity of RLS symptoms (quantified by the IRLS score) and the examined variables. Finally, multiple linear regression analysis was used to determine the factors associated with HRQoL. All analyses were carried out using the Statistical Package for the Social Sciences software (SPSS for Windows, version 19.0, Chicago, Illinois). Data are presented as mean ± SD (95% Confidence Intervals) and the level for statistical significance was set at $P \leq 0.05$.

Results

The prevalence of RLS among this sample of relapsing-remitting MS patients was 20%. The patients' characteristics divided into two groups according to RLS diagnosis are presented in Table 1. None patient experienced RLS symptoms before the onset of Multiple Sclerosis. Iron values were lower in the RLS group compared to the MS-RLS- group ($p = 0.009$). In contrast, ferritin levels did not differ between the two groups ($p = 0.870$).

The patients of the RLS group were found to have significantly worse score in the mental component of the SF-36 questionnaire, in the PSQI and BDI ($p < 0.05$) (Table 2).

The patients' data regarding functional capacity and body composition are presented in Table 3. Performance in the sit to stand tests was worse in the MS-RLS+ group ($p < 0.05$) whereas significantly higher values were observed in the same group in regards to total body fat, trunk fat and abdominal girth ($p < 0.05$).

Moreover, within the MS-RLS+ group, IRLS score was positively associated with BMI (r = 0.295, p= 0.038), PSQI (r= 0.501, p= 0.000), BDI (r= 0.477, p= 0.000), EDSS score (r= 0.349, p= 0.013), STS-5 (r= 0.395, p= 0.005), total body fat (r= 0.390, p= 0.005), trunk fat (r= 0.361, p= 0.010) and fatigue index (r= 0.537, p= 0.000). Negative correlations were observed between the IRLS score and iron levels (r= -0. 408, p= 0.04), the physical (r= -0. 370, p= 0.008) and mental (r= -0.327, p= 0.021) component scores and the total score (r= -0.347, p= 0.014) of the SF-36 questionnaire, STS-30 (r= -0.344, p= 0.014) and STS-60 (r= -0.442, p= 0.001).

IRLS score, STS-5 and TUG as indices of functional capacity, PSQI, BDI, fatigue index and iron levels were included as independent variables in the linear multiple regression analysis to identify the factors associated with the total score of the SF-36 questionnaire. Iron levels were found to be inversely associated with SF-36 total score (r^2= -0.446, p= 0.004) whilst a trend towards significance was found in regards to IRLS score (r^2= -0.320, p= 0.071) and fatigue index (r^2= -0.387, p= 0.062) (Table 4).

Discussion

In the current study we firstly present data regarding functional capacity levels of MS patients with and without RLS and data regarding RLS in MS patients in the Cyprus area. We observed that the MS patients with RLS experience even further impairments in depression symptoms, sleep quality, functional capacity and therefore greater fatigue and lower health-related quality of life levels compared to MS patients without RLS. Moreover, the patients with RLS were found to have significantly higher total and trunk fat levels.

Sleep disorders reported to be highly prevalent in the MS population. A recent meta-analysis and systematic review article report that the prevalence of RLS in the MS population varies between 13.3% to 65.1%, partially depending on the method of assessment [6]. By using a face to face interview, the prevalence of RLS in our MS population was 20%. Idiopathic etiology RLS has been excluded since none of the patient experienced RLS symptoms before the onset of Multiple Sclerosis.

Fatigue is considered to be one of the main problem that the MS patients facing, affecting their quality of life and general wellbeing. Fatigue has been proposed to be multifactorial in the MS population [20]. In the last years, there are a growing number of published studies regarding the association between sleep disorders such as RLS and fatigue in MS patients. Sleep is well established as a key-factor for fatigue and tiredness in the MS population [20]. We observed that the patients with RLS experience significantly poorer sleep quality compared to the patients without RLS, confirming previous studies [9]. We should note that according to the PSQI observed in this study, the patients with RLS can be classified as patients with poor sleep quality. In the current study, fatigue index score in the MS-RLS+ patient is above the cut-off points of fatigue and was found to be significantly higher in the MS-RLS+ group, whilst a strong correlation was found between the severity of RLS symptoms and fatigue index. Those data are in line with previous studies in which RLS presence was associated with greater fatigue in MS patients [6, 9, 21]. The greater levels of fatigue of the MS patients with RLS can be partially explained by the negative effects of the syndrome on sleep, functional capacity and depression levels revealed by the outcomes of the current study, confirming previous findings [20].

Multiple Sclerosis is a neurological disease which is associated with long-term physical and functional disability. Levels of disability were found to be significantly higher in the patients with RLS compared with the patients without RLS, whilst the RLS severity was positively associated with the EDSS score confirming previous data [22]. Until now, no other evidence exists regarding the potential effect of RLS on functional capacity levels in MS patients. Our findings suggest a negative effect of the syndrome on functional capacity as expressed by the patient's performance in a battery of functional tests. A closer view to the functional capacity data reveal that the patients with RLS performed worse only in the functional tests in which lower extremities strength and power are considered to be the key factor performance parameters such as the "sit to stand" tests. Data derived by patients with uremic RLS revealed increased muscle atrophy in the thigh muscles [23], whilst muscle biopsies from idiopathic RLS patients reveal significant capillary remodelling in the morphology of the tibialis anterior muscle of idiopathic RLS patients [24]. Indeed in the later study, aerobic performance as assessed by a cycle ergometer test was found to be significantly decreased in the RLS patients compared to age-matched individuals without RLS. In addition, the greater fatigue and the poorer sleep quality of the MS-RLS+ patients may explain the differences between the two groups in regards to functional capacity.

It is well known that HRQoL is impaired in the Multiple Sclerosis patients. Various factors have been reported to be associated with the impaired HRQoL of the MS population including fatigue and depression, sleep and physical disability [8]. Surprising, and as stated also in a recent systematic review [6], no cross-sectional studies are available in regards to examining potential differences in HRQoL between MS patients with and without RLS. According to our data, the patients of the RLS group were found to experience further impairments on various factors which are known to be associated with HRQoL in the MS population such as sleep, depression, functional capacity, confirming previous findings [9]. We should note that the score observed in the current study in regards to the BDI questionnaire of the MS-RLS+ patients indicated patients with mild depression. Daily sleepiness status did not found to differ between the patients with and without RLS, in contrast to other studies [21], however supporting other studies in RLS patients [23]. Finally, the multiple linear regression analysis performed in the current study revealed that RLS severity, sleep quality and fatigue levels were independently associated with HRQoL in this sample of relapsing-remitting MS patients.

According to our knowledge, these are the first data regarding body composition (i.e. body fat) in MS patients with and without RLS. Interestingly, we found that the MS-RLS+ group exhibited a greater level of both total body fat and trunk fat compared to patients without RLS. In addition, a trend towards significance was found in regards to BMI, which appear higher in the MS-RLS+ group. Published evidence exists regarding possible associations between RLS and obesity indices such as BMI in MS [25] and non-MS populations [26, 27], however, other studies did not confirm such an association [23]. The high fat levels of the RLS patients may explained by several factors associated with RLS, including nocturnal eating [28], sleep loss and sleep deprivation-related metabolic and hormonal abnormalities [29]. In addition, as reported above, the patients with RLS were found to experience high fatigue levels. It is possible that fatigue acted as a barrier to exercise and physical activity leading to inactivity and fat gain. Moreover, RLS in MS patients is more frequent in subjects with frequent in subjects with spinal lesion which could reduce mobility [30]. We should note that MS patients having such high total body fat and trunk fat levels are considered to be at high risk for developing cardiovascular diseases and metabolic syndrome [31]. More research is needed in order to clarify the association between fat levels and RLS in the MS population.

Low iron levels have been associated with both presence and severity of RLS in idiopathic patients [32]. We found that iron levels were significantly lower in the RLS group compared to the non-RLS group, confirming previous studies[6]. Moreover, according to the data of the current study, the severity of RLS correlated with iron levels. However, we should note that other studies did not confirm any association between iron levels and RLS presence and severity in MS patients [4]. On the other hand, ferritin levels did not differ between the two groups. Taking into account the controversy in regards to the relationship between RLS and iron in MS patients and the fact that ferritin levels in the current study did not differ between the two groups we assume that this form of RLS associated with MS may doesn't depend on iron but on other MS-related pathophysiological characteristics such as Central Nervous System lesions (i.e. a real secondary RLS form).

According to the literature, interventions resulted to the management of the RLS symptoms could result among others in enhancements of quality of life, depression and overall health parameters [2]. Taking into account the high prevalence of RLS in the MS patients and the negative effect of the syndrome on various aspects of quality of life, health and wellbeing, early diagnosis and successful management of RLS should be targets of the neurologists and MS care providers.

Unfortunately, in the current study we did not assess factors which are associated to the development of chronic diseases such as cardiovascular diseases, diabetes, hypertension and hypercholesterolemia. Therefore we lost the opportunity to examine whether the MS patients with RLS may experience increased risk for developing those diseases. Moreover, we should note that only patients with Relapsing-Remitting MS participated in the current study. Is still not clear whether the clinical subtype of MS is affecting the presence of RLS in the MS population. Published data reveal that primary progressive MS patients may exhibit an increased risk for RLS compared to the other MS subtypes [4, 22]. On the other hand, other studies observed higher prevalence of RLS in Relapsing-Remitting MS [33] and in secondary progressive MS [34].

In conclusion, the findings of the current study indicate the negative impact of RLS on sleep quality, depression, fatigue, health-related quality of life and functional capacity of MS patients whilst an association between RLS and cardiovascular disease risk factors such as high total body and trunk fat levels is uncovered as well. On the other hand, undertreatment of RLS in MS population is very common. Future prospective interventional studies are warrant to understand whether RLS treatment in these patients will improve fatigue, overall health and quality of life of the MS patients who suffer also from RLS as well as to verify if losing weight and body fat might be a therapeutical option to reduce the severity of RLS symptoms and therefore reduce fatigue and improve health-related quality of life.

References

1. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014 Aug;15(8):860-73. doi: 10.1016/j.sleep.2014.03.025. PubMed PMID: 25023924.
2. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, et al. Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review. Kidney Int. 2014 Jun;85(6):1275-82. doi: 10.1038/ki.2013.394. PubMed PMID: 24107848.
3. Salminen AV, Rimpila V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). Neurology. 2014 May 27;82(21):1856-61. doi: 10.1212/WNL.0000000000000454. PubMed PMID: 24789861.
4. Manconi M, Ferini-Strambi L, Filippi M, et al. Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. Sleep. 2008 Jul;31(7):944-52. PubMed PMID: 18655317; PubMed Central PMCID: PMC2491510. eng.
5. Aydar G, Kurt S, Karaer Unaldi H, et al. Restless legs syndrome in multiple sclerosis. Eur Neurol. 2011;65(5):302-6. doi: 10.1159/000327315. PubMed PMID: 21576965.
6. Sieminski M, Losy J, Partinen M. Restless legs syndrome in multiple sclerosis. Sleep Med Rev. 2015 Aug;22:15-22. doi: 10.1016/j.smrv.2014.10.002. PubMed PMID: 25454673.
7. Brass SD, Duquette P, Proulx-Therrien J, et al. Sleep disorders in patients with multiple sclerosis. Sleep Med Rev. 2010 Apr;14(2):121-9. doi: 10.1016/j.smrv.2009.07.005. PubMed PMID: 19879170.
8. Lobentanz IS, Asenbaum S, Vass K, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand. 2004 Jul;110(1):6-13. doi: 10.1111/j.1600-0404.2004.00257.x. PubMed PMID: 15180801.
9. Moreira NC, Damasceno RS, Medeiros CA, et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. Braz J Med Biol Res. 2008 Oct;41(10):932-7. PubMed PMID: 19030714.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52. PubMed PMID: 6685237.
11. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med. 2003 Mar;4(2):121-32. PubMed PMID: 14592342.

12. Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000 Dec 15;25(24):3130-9. PubMed PMID: 11124729; eng.
13. Beck AT, Guth D, Steer RA, et al. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour research and therapy. 1997 Aug;35(8):785-91. PubMed PMID: 9256522.
14. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213. doi: 0165-1781(89)90047-4 [pii]. PubMed PMID: 2748771; eng.
15. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121-3. PubMed PMID: 2803071; eng.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5. PubMed PMID: 1798888.
17. Koufaki P, Mercer T. Assessment and monitoring of physical function for people with CKD. Adv Chronic Kidney Dis. 2009 Nov;16(6):410-9. doi: S1548-5595(09)00169-4 [pii]

10.1053/j.ackd.2009.08.010. PubMed PMID: 19801131; eng.
18. Enright PL. The six-minute walk test. Respir Care. 2003 Aug;48(8):783-5. PubMed PMID: 12890299.
19. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991 Feb;39(2):142-8. PubMed PMID: 1991946.
20. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep. 2010 Aug;33(8):1061-7. PubMed PMID: 20815187; PubMed Central PMCID: PMC2910465.
21. Carnicka Z, Kollar B, Siarnik P, et al. Sleep disorders in patients with multiple sclerosis. J Clin Sleep Med. 2015 May;11(5):553-7. doi: 10.5664/jcsm.4702. PubMed PMID: 25700869; PubMed Central PMCID: PMC4410929.
22. Manconi M, Fabbrini M, Bonanni E, et al. High prevalence of restless legs syndrome in multiple sclerosis. Eur J Neurol. 2007 May;14(5):534-9. PubMed PMID: 17437613.
23. Giannaki CD, Sakkas GK, Karatzaferi C, et al. Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome. PLoS One. 2011;6(10):e25180. doi: 10.1371/journal.pone.0025180

PONE-D-11-12475 [pii]. PubMed PMID: 21984901; PubMed Central PMCID: PMC3184961. eng.
24. Larsson BW, Kadi F, Ulfberg J, et al. Skeletal muscle morphology in patients with restless legs syndrome. Eur Neurol. 2007;58(3):133-7. PubMed PMID: 17622717.
25. Miri S, Rohani M, Sahraian MA, et al. Restless legs syndrome in Iranian patients with multiple sclerosis. Neurol Sci. 2013 Jul;34(7):1105-8. doi: 10.1007/s10072-012-1186-7. PubMed PMID: 22960874.
26. Winter AC, Schurks M, Glynn RJ, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in women. Am J Med. 2013 Mar;126(3):220-7, 227 e1-2. doi: 10.1016/j.amjmed.2012.06.040. PubMed PMID: 23410562; PubMed Central PMCID: PMC3574635.
27. Yildiz D, Buyukkoyuncu N, Kilic AK, et al. Obesity: a possible risk factor for restless legs syndrome. Neurological research. 2017 Dec;39(12):1044-1048. doi: 10.1080/01616412.2017.1376394. PubMed PMID: 28944745.
28. Provini F, Antelmi E, Vignatelli L, et al. Association of restless legs syndrome with nocturnal eating: a case-control study. Mov Disord. 2009 Apr 30;24(6):871-7. doi: 10.1002/mds.22460. PubMed PMID: 19199358.

29. Knutson KL, Spiegel K, Penev P, et al. The metabolic consequences of sleep deprivation. Sleep Med Rev. 2007 Jun;11(3):163-78. doi: 10.1016/j.smrv.2007.01.002. PubMed PMID: 17442599; PubMed Central PMCID: PMC1991337.
30. Manconi M, Rocca MA, Ferini-Strambi L, et al. Restless legs syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. Mult Scler. 2008 Jan;14(1):86-93. PubMed PMID: 17942519.
31. Wens I, Dalgas U, Stenager E, et al. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis - a systematic review. Mult Scler. 2013 Oct;19(12):1556-64. doi: 10.1177/1352458513504252. PubMed PMID: 24048545.
32. Allen RP, Earley CJ. The role of iron in restless legs syndrome. Mov Disord. 2007 Jun 12;22(S18):S440-S448. PubMed PMID: 17566122.
33. Douay X, Waucquier N, Hautecoeur P, et al. [High prevalence of restless legs syndrome in multiple sclerosis]. Revue neurologique. 2009 Feb;165(2):194-6. doi: 10.1016/j.neurol.2008.06.001. PubMed PMID: 18808767.
34. Vavrova J, Kemlink D, Sonka K, et al. Restless legs syndrome in Czech patients with multiple sclerosis: an epidemiological and genetic study. Sleep Med. 2012 Aug;13(7):848-51. doi: 10.1016/j.sleep.2012.03.012. PubMed PMID: 22609020.

Tables and Figures

Table 1- Patient's characteristics divided in two groups according to RLS diagnosis.

Variables	**MS-RLS+**	**MS-RLS-**	**p value**
N	10	40	-
Female / Male	7/3	17/23	0.470[a]
Age (yr)	39.9±9.2	38.1±6.5	0.481
Weight (kg)	79.0±13.3	69.7±15.9	0.095
Height (cm)	167.3±9.9	165.6±7.2	0.547
IRLS score	19.9±5.4	-	-
EDSS score	3.0±1.2	2.2±0.9	**0.043**
Iron (µg/dL)	55.0±24.9	86.5±34.1	**0.009**
Ferritin (ng/ml)	76.0±51.5	82.7±73.4	0.896[b]
Hct	40.1±2.7	40.1±3.1	0.983
Hb (g/dL)	13.2±1.4	13.3±1.3	0.830

All data are mean ± SD. Abbreviations: IRLS, International Restless Legs Syndrome severity scale; EDSS, expanded disability status scale score, Hct, haematocrit; Hb, haemoglobin.

[a]For categorical data a chi-square test was performed

[b] For data without normal distribution a Mann-Whitney *U* test was performed

Table 2- Health-related quality of life, depression, fatigue, daytime sleepiness and sleep quality data divided in two groups according to RLS diagnosis.

Variables	**MS-RLS+**	**MS-RLS-**	**p value**
SF-36 MCS 95% CI	58.5±21.7 42.9 to 74.1	75.0±19.6 68.7 to 81.2	**0.011**[b]
SF-36 PCS 95% CI	61.2±22.2 45.3 to 77.1	73.3±17.2 67.7 to 78.8	0.083[b]
SF-36 total score 95% CI	62.7±19.8 48.5 to 76.8	76.1±18.3 70.2 to 81.9	**0.047**
Pittsburgh Sleep Quality Index 95% CI	7.0±5.6 2.9 to 11.1	2.9±2.4 2.1 to 3.7	**0.004**[b]
Epworth Sleepiness Scale 95% CI	5.2±6.8 0.2 to 10.1	3.2±4.2 1.8 to 4.5	0.246
Beck Depression Inventory 95% CI	16.5±17.2 4.1 to 28.8	4.2±6.4 2.1 to 6.3	**0.005**[b]
Fatigue Severity Scale Index 95% CI	5.8±0.9 5.1 to 6.5	4.3±1.0 4.0 to 4.7	**0.000**

All data are mean ± SD (95% Confidence Intervals). SF-36, 36-Item Short Form Health Survey; MCS, mental component score; PCS, physical component score

[b] For data without normal distribution a Mann-Whitney *U* test was performed

Table 3- Functional capacity and body composition data divided in two groups according to RLS diagnosis.

Variables	**MS-RLS+**	**MS-RLS-**	**p value**
Functional capacity data			
STS- 5 (sec) 95% CI	14.4±3.4 11.9 to 16.8	11.9±2.6 11.0 to 12.7	**0.016**
STS-30 (rep) 95% CI	10.9±2.2 9.3 to 12.4	12.8±2.4 12.1 to 13.6	**0.028**
STS-60 (rep) 95% CI	20.6±4.6 17.2 to 23.9	25.9±4.8 24.3 to 27.5	**0.003**
Six-minute walk test (m) 95% CI	415.8±121.5 328.8 to 502.7	443.4±97.1 412.4 to 474.5	0.447
TUG test (sec) 95% CI	9.3±1.8 8.0 to 10.6	8.5±1.5 8.0 to 9.1	0.169
Body composition data			
Total fat (%) 95% CI	34.4±9.2 27.8 to 41.1	28.1±7.4 25.7 to 30.5	**0.026**
Abdominal Girth (cm) 95% CI	104.8±14.8 94.1 to 115.4	92.3±13.9 87.8 to 96.8	**0.016**
Trunk fat (%) 95% CI	38.6±11.8 30.2 to 47.1	31.0±9.7 27.9 to 34.1	**0.039**
Body Mass Index 95% CI	28.3±5.4 24.3 to 32.2	25.2±5.0 23.6 to 26.8	0.097

All data are mean ± SD (95% Confidence Intervals). P values are adjusted for yrs in dialysis. Abbreviations: STS-5, sit-to- stand test 5-repetitions; STS-60, sit-to- stand test 60 seconds; TUG, timed up and go test

Table 4: Multiple linear regression to evaluate the predictors of health-related quality of life ($r^2 = 0.386$)

Variable	**Coefficient**	**Standard Error**	**p value**
IRLS score	-0.320	0.395	**0.071**
STS-5	-0.052	1.199	0.781
TUG	-0.152	2.008	0.365
PSQI score	0.083	0.795	0.588
EDSS	0.202	2.921	0.210
FSS index score	-0.387	3.140	**0.062**
BDI score	-0.151	0.312	0.382
Iron	-0.446	0.083	**0.004**

Abbreviations: IRLS, International Restless Legs Syndrome severity score; STS-5, sit-to- stand test 5-repetitions; TUG, timed up and go test; PSQI, Pittsburg Sleep Quality Index; EDSS, expanded disability status scale; FSS, fatigue severity scale BDI, Beck Depression Inventory