SERBIAN ARCHIVES OF MEDICINE Est.1872

Address: 1 Kraljice Natalije Street, 11000 Belgrade, Serbia
☎ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Original Article / Оригинални рад

Tatjana Smiljković†, Svetlana Kostić-Dedić,
Vesna Nikolić, Anđela Gavrilović, Sanja Jevđić

Restless Legs Syndrome in Patients with Distal Diabetic Polyneuropathy

Синдром немирних ногу код оболелих с дисталном дијабетичном полинеуропатијом

University Medical Center Zvezdara, Department of Neurology, Belgrade, Serbia

Received: October 2, 2017
Revised: November 14, 2017
Accepted: November 16, 2017
Online First: December 8, 2017
DOI: https://doi.org/10.2298/SARH171002201S

* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

† **Correspondence to:**
Tatjana SMILJKOVIĆ
University Medical Center Zvezdara, Presevska 31, 11000 Belgrade, Serbia
E-mail: **ttanjasmiljkovic@yahoo.co.uk**

Restless Legs Syndrome in Patients with Distal Diabetic Polyneuropathy

Синдром немирних ногу код оболелих с дисталном дијабетичном полинеуропатијом

SUMMARY

Introduction/Objective An association between Restless legs syndrome (RLS) and etiologically different polyneuropathies is well established. However, the investigations about the prevalence of RLS in diabetic polyneuropathy (DPN) led to controversy.

Our study objective was to determine the frequency of RLS in patients with distal symmetrical polyneuropathy in patients with diabetes and identify possible risk factors for its occurrence in this group of patients.

Method We investigated 101 consecutive patients with distal DPN. RLS was diagnosed according to the International RLS Study Group diagnostic criteria. The distal symmetrical polyneuropathy was confirmed by the electromyoneurographic study performed in each patient.

Results Overall RLS was present in 27 (26.73%) patients. The comparison between patients with and without RLS revealed the RLS+ group included more women than men (14,85 /9.90% vs. 35,64/37,62%,ns), patients were significantly younger (60.58±10.54 vs. 65.57±10.94 years, p≤0.05), sensory polyneuropathy was significantly more common (17/27 vs. 34/74, p≤0.05); the average level of the total Ca serum concentration was higher in the RLS + group than in non-RLS (2.43±0.26 vs 2.28±0.39; p≤0,05). However, multivariate logistic regression analysis did not demonstrate these as significant independent risk factors for RLS in DPN.

Conclusions The RLS is common in DPN and occurs in more than a quarter of these patients. Though sensory forms and higher total serum Ca concentration were associated with RLS, neither of these has been identified as significant single risk factor for the development of RLS in DPN.

Keywords: Restless legs syndrome; diabetes mellitus; polyneuropathy

САЖЕТАК

Увод/Циљ Повезаност синдрома немирних ногу (СНН) са неуропатијама различите етиологије јасно је утврђена. Међутим, резултати истраживања о учесталости СНН код дијабетичне полинеуропатије (ДПН) су контроверзни.

Циљ нашег рада је био да се утврди учесталост СНН код болесника са дисталном дијабетичном полинеуропатијом као и да се установе могући фактори ризика за његову појаву у овој групи оболелих.

Метод Испитивање је обухватило 101 консекутивног оболелог с дисталном ДПН. Дијагноза СНН је постављена на основу критеријума Инернационалне групе за испитивање Синдрома немирних ногу. Сваком болеснику урађено је електромионеурографско испитивање којим је потврђена дијагноза дисталне ДПН.

Резултати СНН је био присутан код 27 (26.73%) болесника у односу на целу групу. Поређење оболелих са (СНН+) и без (СНН-), показало је да у групи СНН+ је било нешто више жена него мушкараца (14,85 /9.90% тј. 35,64/37,62%, нз), оболели су били значајно млађи (60.58±10.54 тј. 65.57± 0.94 година; $p \leq 0.05$); значајно чешћа је била сензитивна полинеуропатија (17/27 тј. 34/74, $p \leq 0.05$) и имали су виши ниво *Ca* у крви у односу на оболеле без СНН-(2.43±0.26 вс 2.28±0.39; $p \leq 0,05$). Међутим, мултиваријантна регресиона анализа није показала да је иједан од њих значајан фактор ризика за појаву СНН код дисталне ДПН.

Закључак СНН чест је код ДПН и јавља се код више од четвртине оболелих. Иако су сензорна форма и повишен ниво укупног *Ca* у серуму били удружени са СНН, ниједан од њих се није издвојио као значајан појединачни фактор ризика за настанак СНН код дисталне ДПН.

Кључне речи: синдром немирних ногу; дијабетес; полинеуропатија

INTRODUCTION

Restless legs syndrome (RLS) causes an irresistible urge to move legs usually accompanied by unpleasant sensations in them; the symptoms occur at rest usually before sleep, and after activity or stretch they subside [1]. Thus far the assumption is that central dopaminergic dysfunction contributes to the disease pathogenesis [2]. The disorder can be primary and secondary. Forty to sixty percent of patients with primary RLS have a positive family history with autosomal dominant inheritance [3]. Secondary RLS can coincide with various conditions such as iron deficiency, low ferritin level, renal

failure, and anemia, especially during pregnancy [4. 5, 6]. An association between RLS and etiologically different polyneuropathies, including diabetic neuropathy, has been suggested in previous studies [7, 8]. However, the investigations about a link between RLS and diabetic neuropathy led to controversy; while some authors found a high prevalence of RLS in diabetic neuropathy [9] others did not [10].

Our study objective was to determine the frequency of RLS in patients with distal symmetrical polyneuropathy in patients with diabetes and identify possible risk factors for its occurrence in this group of patients.

METHODS

The study was conducted at the Clinical Department of Neurology in University Medical Center "Zvezdara". It included 101 consecutive patients with Diabetes mellitus and a confirmed diabetic polyneuropathy. Patients on dialysis, rapidly deteriorating patients, patients with other conditions which could cause RLS, as well as pregnant women, were excluded from the trial. All patients voluntary participated in the study and signed written informed consent.

The original questionnaire (table 1) was used to obtain demographic data and data about related conditions: diabetes, polyneuropathy, and RLS. Relevant essentials for each condition were the age of the onset, the duration of the disease, its course, as well as a temporal relationship between them. Also, other concomitant illnesses and medications were registered.

Table 1. **Questionnaire.**

Name and surname
Gender M F Age at observation (years)
Diabetes mellitus (D.M.)
Age at onset of D.M. (years)
Disease duration of D.M. (years)
Diabetes mellitus type : I II
Diabetes mellitus therapy
Duration of therapy for D.M. (years)
Age at onset of polyneuropathy (years)
Duration of polyneuropathy (years)
Concomitant illness
Blood donors:
YES NO; No. of donations in past 3 years
Blood transfusions:
YES NO, No. of transfusions in past 3 years
Habits:
Coffee intake : YES NO,
Duration of habits (years)
Cup of coffee No/day
Smoking: YES NO,
Duration of habits (years)
Cigarettes No/day
Alcohol: YES NO,
Duration of habits (years)
RLS: YES NO
Duration of RLS symptoms (years)
Age at the onset of RLS (years)
Family history: YES NO

One of the investigators performed clinical neurological examination in all patients. The distal symmetrical polyneuropathy was diagnosed in patients with the clinical finding of the diffuse distal involvement of peripheral nerves on the extremities. The second investigator performed electroneurophysiological study in all patients and confirmed diagnosis of polyneuropathy, using electromyoneurographic criteria [11]. Based on the symptoms, according to Wolf's criteria, polyneuropathy was classified as sensory, motor or sensorimotor [12].

The third neurologist, blinded for the clinical and neurophysiological evaluation, established the diagnosis of RLS. The patients were diagnosed as RLS only if all four diagnostic criteria were present, defined by the International RLS Study Group

(IRLSSG): 1. an urge to move the legs usually accompanied or caused by unpleasant and uncomfortable sensations in the legs; 2. the urge to move or unpleasant sensation begin or worsen during periods of rest or inactivity such as lying or sitting; 3. the urge to move or unpleasant sensation are partially, or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; 4. the urge to move or unpleasant sensations are worse in the evening or at night than during the day or only occur in the evening or night [1]. At the onset of the investigation, new criteria have not been defined [13].

From every patient blood sample was taken and complete blood count, hematocrit, a concentration of hemoglobin, ferritin, iron, electrolytes, BUN, cholesterol, cholesterol fractions and triglycerides were determined.

Statistical analysis included methods of descriptive statistics, Student's t test, and Chi square test. Logistic regression analysis assessed the importance of the risk factors, and odds ratio (OR) measured the effect with a 95% confidence interval (95% CI). A p value of 0.05 or less was considered statistically significant.

RESULTS

The study involved 52 (52.5%) men and 49 (47.5%) women, with a mean age of 64.13±11.02 years. One-third of the patients had DM type I (34/101) and two-thirds had DM type II (67/101) which persisted 12.64± 8.1 years on average. RLS was present in 27 (26.73%) patients, of whom 13 patients had DM type I and 14 patients DM type II.

The comparison between patients with and without RLS was performed (RLS+ and RLS- group, respectively). There were more women than men in RLS+ group (14,85 /9.90% vs. 35,64/37,62%, ns) and this group of patients was significantly younger than patients without RLS (60.58±10.54 vs. 65.57±10.94 years, p≤0.05).

Table 2. Comparission of patients with and without RSL in distal diabetic polyneuropathy.

	RLS+ (n = 27)	RLS- (n = 74)	*p*
Gender (M/F, %)	9.90/14,85	37,62/35,64	ns
Current age	60.58±0.54	65.57±0.94	p<0.05
Typ: DM I / DM II	13/14	21/53	ns
Duration DM	5.56±5.74	12.84±8.72	ns
Duration od polyneuropathy	4.47±3.22	6.05±5.64	ns
MCV	36.38±9.07	36.26±8.14	ns
Latency	5.16±3.89	5.56±4.72	ns
SCV	29.62±10.01	29.75±9.90	ns
Er	4.21±1.21	4.41±0.74	ns
Hct	39.27±4.09	39.14±4.42	ns
Feritin	173.93±189.20	175.87±143.66	ns
Na	140.82±3.49	138.10±8.38	ns
K	5.16±4.14	5.36±4.16	ns
Ca	2.43±0.26	2.28±0.39	p<0,05
Mg	0.94±0.46	0.79±0.081	ns
Cholesterol	5.94±1.50	5.82±1.164	ns
Tryglicerid	2.57±1.87	2.39±1.65	ns

MCV-motor nerve conduction velocities,
SCV- sensitive nerve conduction velocities.

No difference in the type of diabetes, duration of diabetes or duration of diabetic polyneuropathy, was found between the groups (Table 2). However, the type of distal peripheral neuropathy was different:

sensory polyneuropathy was significantly more common in the RLS + group (17/27 vs. 34/74, p≤0.05), while sensorimotor in RLS- patients (10/27 versus 40/74, p ≤ 0.05).

Comparing laboratory parameters, the only statistically significant difference was found in the average level of total Ca serum concentration: it was higher in the RLS + group than in non RLS (2.43±0.26 vs 2.28±0.39; p≤0,05). The complete blood count, iron and ferritin levels, electrolytes, and serum lipids concentrations were not different between the groups (Table 2).

Univariate logistic regression analysis revealed that total Ca serum concentrations (p=0.025) and nerve conduction latency (p=0.048) were associated with RLS. However, multivariate logistic regression analysis did not demonstrate these as significant independent risk factors for RLS in diabetic polyneuropathy.

DISCUSSION

Our results confirmed that RLS was common in patients with diabetic polyneuropathy: almost a quarter of them had RLS (26.73%), which was significantly more than in the general population (7-10%) [14]. According to other studies, the number of patients with polyneuropathy and RLS varies from 5.2% up to 36%, and this difference was the aftermath of diverse study designs [15,16]. However, most studies have shown an alliance between RLS and neuropathy [17, 18, 19], despite whether they analyzed RLS frequency in the patients with neuropathy [7, 16] or the frequency of neuropathy in the patients with RLS [17]. Our results were consistent with the results of Lopes who found RLS in 27 patients from the group of 100 patients with diabetes, and 25 of those 27 patients had neuropathy too [19]. Gemignani et al. reported a somewhat higher frequency of RLS in patients with diabetic neuropathy (33.3%), especially in patients with distal diabetic polyneuropathy [18]. Slightly lower prevalence of the RLS in our group, compared with the results of Gemignani et al., could be explained by the decision to include only patients with electrophysiologically confirmed neuropathy; consequently, the patients with small-fiber neuropathy could not qualify. Other authors, however, did not corroborate the frequency difference of RLS in diabetics and controls [10]. Since patients inform about similar symptoms in neuropathy and RLS, symptoms overlap and RLS could be overlooked in patients with neuropathy. Some authors suggested that in every patient with a suspected neuropathy an interview focused on RLS criteria should be performed [20].

Results of this study showed that RLS is more common in patients with sensory polyneuropathy, the same as previously found by other authors [9], who particularly emphasized the association of RLS and sensory small-fiber neuropathy [18]. The further assumption was that abnormal inputs from the periphery activate spinal generators so that RLS is not exclusively associated with central dopaminergic dysfunction but possibly starts on a different level of the nervous system, either central or peripheral [18].

Our RLS patients were younger than those without RLS. The observation was interesting because, although children may have RLS, epidemiological studies have shown that it occurs most

frequently in the middle-aged and that the incidence rises with age [4]. The results in the literature differ: while some authors concluded that patients with RLS are older than controls [16, 17], others did not find this difference [8, 10, 18, and 21].

In our RLS + group women were slightly more represented, which was determined in the majority of trials [7, 21], although there are papers where there is no difference between genders [16]. Other female patients (without neuropathy) also have RLS more often, but there the connection between RLS and anemia or pregnancy was established [4,5].

We did not find the difference in serum iron and ferritin levels between patients with and without RLS. Numerous studies have suggested the association of iron metabolism and low serum ferritin with RLS, and several studies have shown that severity of RLS correlates with the level of serum ferritin [4]. However, it appears that the RLS+ diabetic population is independent of serum iron and ferritin levels [8, 10, and 21]. We recorded a significantly higher level of total serum Ca in those with RLS. The same was noted in hemodialysis patients and investigators suggested that high serum Ca was possibly connected to the patophysiology of RLS [22]. The exact significance of this result in diabetic polyneuropathy is not clear and further tests are required to confirm and establish this result.

Though univariate logistic regression analysis has shown association between serum calcium concentrations and nerve conduction latency with RLS, multivariate logistic regression analysis did not isolate any of the investigated factors as significant single risk factor for the development of RLS in distal diabetic polyneuropathy. Investigation of possible risk factors for occurrence of RLS in diabetics disclosed in some studies, peripheral neuropathy to be the only risk factor for the occurrence of RLS [19,21], while others revealed none [10].

Our study had several limitations including a relatively small sample and exclusion of patients with sensory small-fiber neuropathy. Anyway, we believe the research is important because only a few in our country deal with this problem.

CONCLUSIONS

The RLS is common in diabetic polyneuropathy and occurs in more than a quarter of these patients. Though sensory polyneuropathy and higher total serum Ca concentration were associated with RLS, neither of these has been identified as significant single risk factor for the development of RLS in diabetic polyneuropathy. Further studies are needed to clarify the real association between Ca serum concentration and RLS in diabetic polyneuropathy.

REFERENCES:

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplasir J. Restless legs syndrome:diagnostic criteria, special considerations, and epidemiology: a report from resless legs syndrome diagnosis and epidemiology workshop at the National Institute of Health. Sleep Med. 2003; 4: 101–19.
2. Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. Lancet Neurol. 2005; 4:465-75. [PMID: 16033689]

3. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. Brain. 2003; 126: 1485–92.
4. Zucconi M, Ferini-Strambi. Epidemiology and clinical findings of restless legs syndrome. Sleep Med. 2004; 5: 293–9.
5. Srivanitchapoom P, Pandey S, Hallet M. Restless legs syndrome and pregnancy: a review. Parkinsonism Relat Disord. 2014; 20(7): 716–22.
6. Gigli GL, Adorati M, Dolso P, Piani A,Velnete M, Brotini S, et al. Restless legs syndrome in end-stage renal disease. Sleep med. 2004; 5(3): 309–15.
7. Gemignani F, Brindani F, Negrotti A, Vitetta F, Alfieri S, Marbini A. Restless Legs Syndrome and Polyneuropathy. Mov Disord. 2006; 21: 1254–7.
8. Luigetti M, Del Grande A, Testani E, Bisogni G, Losurdo A, Giannantoni NM, et al. Restless leg Syndrome in Different Types of Demyeliniating neuropathies: A Single-Center Pilot Study. J Clin Sleep Med. 2013; 9(9): 945–9.
9. Gemignani F, Brindani F, Negrotti A, Vitetta F, Marbini A, Calzetti S. Restless Legs Syndrome in diabetic neuropathy: a frequent manifestation of small fiber neuropathy. J Peripher Nerv Syst. 2007; 12: 50–3.
10. Scomro RP, Ludwig S, Salamon E, Kryger MH. Complaints and restless legs syndrome in adult type 2 diabetics. Sleep Med. 2001; 2: 417–22.
11. Cvijanović M, Ilin M, Slankamenac P, Banić Horvat S, Jovin Z. The sensitivity of electromyoneurography in the diagnosis od diabetic polyneuropathy. Med Pregl 2011; 64(1–2): 11–14.
12. Wolfe GI, Baker NS, Amato AA, Jacskon CE, Nations SP, Saperstein DS, et al. Chronic cryptogenic sensory polyneuropathy. Arch Neurol. 1999; 56: 540–7.
13. Allen RP, Picchietti D, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs Syndrome Study Group. Restless legs syndrome /Willis-Ekbom disease diagnostic criteria: update International restless Legs Syndrome Study Group (IRLSSG) consensus criteria-history, rationale, description and significance. Sleep Med. 2014; 15: 860–73.
14. Hogl B, Kiechl S, Willeit J, Saletu M, Frauscher B, Seppi K, et al. Restless legs syndrome. A community-based study prevalence, severity and risk factors. Neurology. 2005; 64: 1820–924.
15. Rutke SB, Matheson JK, Logigian EL. Restless legs syndrome in patients with polyneuropathy. Muscle Nerve. 1996; 19: 670–2.
16. Cho YW, Na GY, Lim JG, Kim SH, Kim SH, Early CJ, et al. Prevalence and clinical characteristics of restless legs syndrome in diabetic peripheral neuropathy: comparison with chronic osteoarthritis. Sleep Med. 2013; 14: 1387–92.
17. Bastia JK, Bhoi SK, Kalita J, Misra EK. Neuropathy in a cohort of restless leg syndrome patients. J Clin Neurosci. 2015; 22: 1314–8.
18. Gemingnani F, Vitetta F, Brindani F, Contini M, Negrotti A. Painful polyneuropathy associated with restless legs syndrome. Sleep Med. 2013; 14: 79–84.
19. Lopes L, Linc C de MM, Adeodato V, Quental D, De Bruin PFC, Montenegro RM, et al. Restless legs Syndrome and Quality of Sleep in Type 2 Diabetes. Diabetes Care. 2005; 11(28): 2633–6.
20. Nineb A, Rosso C, Dumurgier J, Nordine T, Lefaucheur J-P, Creange A. Restless legs syndrome is frequently overlooked in patients being evaluated for polyneuropathies. Eur J of Neurol. 2007; 14: 788–92.
21. Merlino G, Fratticci L, Valente M, Del Guidice A, Noacco C, Dolso P, et al. Association of Restless Legs Syndrome in Type 2 Diabetes : A case Control Study. Sleep. 2007; 30(7): 866–71.
22. Kawauchi A, Inoue Y, Hashimoto T, Tachibana N, Shirakawa S, Mizutani Y et al. Restless legs syndrome in hemodyalisis patients: health-realted quality of life and laboratory data analysis. Clin Nephrol. 2006; 66(6): 440–6.

