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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Restless legs syndrome in patients with distal diabetic polyneuropathy

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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 (DP) have 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 DP. 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 that the RLS+ group included more women than men (14.85/9.90% *vs.* 35.64/37.62%, non-significant), patients were significantly younger (60.58 ± 10.54 *vs.* 65.57 ± 10.94 years, $p \leq 0.05$), sensory polyneuropathy was significantly more common (17/27 *vs.* 34/74, $p \leq 0.05$); the average level of the total serum calcium concentration was higher in the RLS + group than in non-RLS (2.43 ± 0.26 *vs.* 2.28 ± 0.39; $p \leq 0.05$). However, multivariate logistic regression analysis did not demonstrate these as significant independent risk factors for RLS in DP.
Conclusions RLS is common in DP and occurs in more than a quarter of these patients. Though sensory forms and higher total serum calcium concentration were associated with RLS, neither of these has been identified as a significant single risk factor for the development of RLS in DP.
Keywords: restless legs syndrome; diabetes mellitus; polyneuropathy

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 an activity or stretching 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 has led to controversy; while some authors found a high prevalence of RLS in diabetic neuropathy, others did not [9, 10].

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

METHODS

The study was conducted at the Clinical Department of Neurology of the University Medical Center Zvezdara. It included 101 consecutive patients with diabetes mellitus and confirmed diabetic polyneuropathy. Patients on dialysis, rapidly deteriorating patients, patients with other conditions that could cause RLS, as well as pregnant women, were excluded from the study. 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 at the time 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.

One of the investigators performed clinical neurological examination of all the 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 an electroneurophysiological study in all the patients and confirmed the diagnosis of polyneuropathy, using electromyoneurographic

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Table 1. Questionnaire

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

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: 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 begins or worsens during periods of rest or inactivity, such as lying down or sitting; 3. the urge to move or an 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 stronger in the evening or at night than during the day, or only occur in the evening or at night [1]. At the onset of the investigation, new criteria have not been defined [13].

A blood sample was taken from every patient and complete blood count, hematocrit, concentration of hemoglobin, ferritin, iron, electrolytes, blood urea nitrogen, cholesterol, cholesterol fractions, and triglycerides were determined.

Statistical analysis included methods of descriptive statistics, Student's t-test, and χ^2 test. Logistic regression analysis assessed the importance of the risk factors, and odds ratio measured the effect with a 95% confidence interval. 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 diabetes mellitus type I (34/101) and two thirds had diabetes mellitus 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 diabetes mellitus type I and 14 patients had diabetes mellitus type II.

The comparison between patients with and without RLS was performed (RLS+ and RLS- group, respectively). There were more women than men in the RLS+ group (14.85/9.90% *vs.* 35.64/37.62%, non-significant), and this group of patients was significantly younger than patients without RLS (60.58 ± 10.54 *vs.* 65.57 ± 10.94 years, $p \leq 0.05$).

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

Table 2. Comparison of patients with and without restless legs syndrome in distal diabetic polyneuropathy

Parameter	RLS+ (n = 27)	RLS- (n = 74)	p
Sex M/F	10/15	38/36	ns
Current age (mean ± SD, years)	60.58 ± 10.54	65.57 ± 10.94	$p \leq 0.05$
DM type I/II	13/14	21/53	ns
Duration DM (mean ± SD, years)	5.56 ± 5.74	12.84 ± 8.72	ns
Duration of polyneuropathy (mean ± SD, years)	4.47 ± 3.22	6.05 ± 5.64	ns
MCV (mean ± SD, cm)	36.38 ± 9.07	36.26 ± 8.14	ns
Latency (mean ± SD, cm)	5.16 ± 3.89	5.56 ± 4.72	ns
SCV (mean ± SD, cm)	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
Ferritin	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+	2.43 ± 0.26	2.28 ± 0.39	$p \leq 0.05$
Mg	0.94 ± 0.46	0.79 ± 0.081	ns
Cholesterol	5.94 ± 1.50	5.82 ± 1.164	ns
Triglyceride	2.57 ± 1.87	2.39 ± 1.65	ns

RLS – restless legs syndrome; DM – diabetes mellitus; SD – standard deviation; ns – non-significant; MCV – motor nerve conduction velocities; SCV – sensitive nerve conduction velocities; Hct – hematocrit; Er – erythrocytes

peripheral neuropathy was different: sensory polyneuropathy was significantly more common in the RLS+ group (17/27 *vs.* 34/74, $p \leq 0.05$), while sensorimotor polyneuropathy was significantly more common in the RLS- patients (10/27 *vs.* 40/74, $p \leq 0.05$).

Comparing laboratory parameters, the only statistically significant difference was found in the average level of total serum calcium concentration: it was higher in the RLS+ group than in the non-RLS patients (2.43 ± 0.26 *vs.* 2.28 ± 0.39, $p \leq 0.05$). 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 serum calcium 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, despite whether they analyzed RLS frequency in patients with neuropathy or the frequency of neuropathy in patients with RLS [7, 16–19]. Our results were consistent with the results of Lopes et al. [19], who found RLS in 27 patients from the group of 100 patients with diabetes, and 25 of those 27 patients had neuropathy as well. Gemignani et al. [18] reported a somewhat higher frequency of RLS in patients with diabetic neuropathy (33.3%), especially in patients with distal diabetic polyneuropathy. Slightly lower prevalence of RLS in our group, compared with the results of Gemignani et al. [18], 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]. 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, others did not find this difference [8, 10, 16, 17, 18, 21].

In our RLS + group, women were slightly more represented, which was determined in the majority of trials, although there are papers where there is no difference between sexes [7, 16, 21]. Other female patients (without neuropathy) also have RLS more often, but 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 the 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, 21]. We recorded a significantly higher level of total serum calcium in those with RLS. The same was noted in hemodialysis patients and investigators suggested that high serum calcium was possibly connected to the pathophysiology 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 an association between serum calcium concentrations and nerve conduction latency with RLS, multivariate logistic regression analysis did not isolate any of the investigated factors as a significant single risk factor for the development of RLS in distal diabetic polyneuropathy. Investigation of possible risk factors for the occurrence of RLS in diabetics in some studies disclosed peripheral neuropathy to be the only risk factor for the occurrence of RLS, while others revealed none [10, 19, 21].

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

CONCLUSION

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

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Синдром немирних ногу код оболелих од дисталне дијабетичне полинеуропатије

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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 Интернационалне 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 је у групи СНН+ било нешто више жена него мушкараца (14,85/9,90% тј. 35,64/37,62%), 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 према 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 је чест 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