Association of Restless Legs Syndrome in Type 2 Diabetes: A Case-Control Study

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Study Objective: To look for an association between restless legs syndrome (RLS) and type 2 diabetes in a case-control study; to analyze the characteristics of RLS in diabetic patients; and to identify possible risk factors for the development of RLS in diabetic patients.

Design: A case-control study.

Setting: Diabetic outpatient clinic of a major university hospital.

Participants: One hundred twenty-four consecutive outpatients with diabetes and 87 consecutive controls with a previous diagnosis of other endocrine disease.

Interventions: RLS was diagnosed using the criteria of the International RLS Study Group, and severity of RLS was assessed using the International RLS Study Group Rating Scale. Characteristics of RLS and several laboratory parameters were investigated in diabetic patients and controls affected by the sleep disorder. A clinical diagnosis of polyneuropathy was assessed to evaluate its role as a risk factor for RLS in diabetic patients.

Measurement and Results: RLS was diagnosed in 22 diabetic patients (17.7%) and in only 5 controls (5.5%), 3 of whom had pituitary and 2 had adrenal gland disorders, and RLS was independently associated with type 2 diabetes (P < 0.04). Even if a clinical diagnosis of polyneuropathy was made in only 27% of diabetic patients affected by RLS, after multivariate logistic regression, the presence of polyneuropathy was the only variable associated with RLS in diabetics (odds ratio, 7.88; 95% confidence interval, 1.34-46.28; P < 0.02). RLS in diabetics showed a frequency of positive family history lower than that known for primary RLS, showed a late age of onset, and manifested itself after the diagnosis of diabetes was made.

Conclusions: This is the first controlled study confirming a significant association between RLS and type 2 diabetes. In diabetic patients, polyneuropathy represents the main risk factor for RLS. However, polyneuropathy only partially explains the increased prevalence of RLS in type 2 diabetics. Clinical characteristics of RLS in diabetic patients are those of a secondary form.

Keywords: RLS, type 2 diabetes, epidemiology, polyneuropathy, case-control study

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RESTLESS LEGS SYNDROME (RLS) IS AN INTRINSIC SLEEP DISORDER IN WHICH PATIENTS DESCRIBE AN URGE TO MOVE THEIR LEGS OR OTHER EXTREMITIES during rest. This may be accompanied by unpleasant sensations that are temporarily relieved by movement. Typically, the sensory-motor complaints of RLS arise or worsen during the night, showing a circadian pattern.

RLS discomfort leads to a severe difficulty in initiating and maintaining sleep due to the fact that the motor activity carried out by patients in search of relief prolongs sleep latency and the frequent association of periodic limb movements during sleep causes arousals. Consequently, patients complain of insufficient and unsatisfactory sleep and of altered daytime functioning.

Several conditions (such as iron deficiency,[1] uremia,[2] pregnancy,[3] polyneuropathy,[4] and rheumatoid arthritis[5]), which account for about one quarter of the clinical cases, have been associated with RLS, configuring a secondary or symptomatic form. With reference to type 2 diabetes mellitus, there are still no rigorous studies investigating the association between the endocrine disease and RLS.[6,7] An association between the 2 disturbances can be suspected, since both clinical conditions show at least 1 possible common pathophysiologic mechanism (polyneuropathy) and diabetic patients are more at risk of presenting RLS than is the general population.[8] The aims of this investigation were: (1) to look for an association between RLS and type 2 diabetes in a case-control study, (2) to analyze the characteristics of RLS in diabetic patients, and (3) to identify possible risk factors for the development of RLS in diabetic patients.

METHODS

Patient selection

In our study, 124 consecutive patients with type 2 diabetes attending the diabetes center of the Udine University Hospital, Italy, were recruited from March 2005 to July 2005. The control group consisted of 87 consecutive patients who were attending the endocrinology department for regular follow-up of previously diagnosed and treated endocrine disorders other than diabetes (pituitary and adrenal glands disorders). The diabetes center and the endocrinology department serve the same health district and the general population. All controls were in an inactive phase of their endocrine disease. In particular, all controls were not requiring any pharmacologic treatment. Subjects younger than 18 years of age were not included in the study. Similarly, pregnant women were excluded because the expected high prevalence of RLS in this specific subgroup of the general population could result in a confounding factor. Clinical conditions considered as exclusion criteria were Parkinson disease; myelopathy; L4, L5, or S1 ra-

diculopathy; and dialysis dependence. A written informed consent was obtained before recruitment.

General Protocol

Records were reviewed and patients were interviewed to obtain information pertaining to demographic aspects, past medical history, and use of medications. In particular, we focused our attention on clinical conditions favouring RLS (anaemia with iron deficiency, hypothyroidism, uremia, and rheumatoid arthritis) and on drugs able to worsen RLS symptoms (antidepressants or antipsychotics) or to improve RLS symptoms (dopaminergic agents, benzodiazepines, and anticonvulsants such as gabapentin, carbamazepine, oxcarbazepine, and valproic acid).

Diabetic patients were investigated for duration, complications (subdivided into microvascular, i.e., retinopathy, nephropathy, and polyneuropathy, and macrovascular, i.e., obliterating arteriopathy of the lower limbs, coronary artery disease, or cerebral vascular disease) and treatment of their endocrine disease.

RLS Protocol

In both the diabetic and control groups, a neurologist certified as a sleep expert by the Italian Association for Sleep Medicine and masked regarding neurologic evaluation established the presence of RLS using the 4 questions proposed by the International Restless Legs Syndrome Study Group.[9] Only the patients who fulfilled all 4 criteria were considered affected by RLS and were requested to answer 10 additional questions in order to assess RLS severity, using the International Restless Legs Syndrome Study Group Rating Scale (IRLS).[10] Presence of RLS symptoms in first-degree relatives was established in all diabetic patients and in controls. Moreover, diabetic patients and controls with RLS were investigated concerning: (1) age of RLS onset and (2) deep or superficial localization and subjective description of RLS symptoms (choosing between *pain*, *burning*, *urge to move*, *electric*, *pulling*, or *other*).[11]

Laboratory Data

Many laboratory parameters were obtained for the all subjects. Blood samples were obtained and analyzed for complete blood count, glucose, total cholesterol, triglycerides, and creatinine in all patients and controls. Levels of glycosylated hemoglobin (HbA1c) were determined only in patients affected by type 2 diabetes. In diabetic patients affected by RLS and in controls diagnosed with RLS, the following laboratory parameters were recorded: folate, vitamin B_{12}, thyroid-stimulating hormone, free triiodothyronine (fT3), and free thyroxine (fT4). Ferritin was measured out in all diabetic patients and in the subgroup of controls affected by RLS. In 3 diabetic patients not affected by RLS, ferritin levels were so high that they were considered outliers, so these data were excluded from the statistical analyses. Two diabetic patients with RLS refused to have their blood drawn.

Evaluation of Polyneuropathy

A neurologist, expert on peripheral nervous system disturbances and masked regarding RLS diagnosis, assessed the subjects' sensory function, distal muscle strength, and deep tendon reflexes, both in diabetic patients and in controls, in order to investigate for the

presence of distal symmetric polyneuropathy. Two polyneuropathy aspects were required for a correct detection of this disturbance. Polyneuropathy had to be "distal," involving those parts most distant from the center of the body, and "symmetric," indicating that signs and symptoms were the same on both sides of the body. Distal sensory function was examined bilaterally using Semmes-Weinstein (SW) filaments and 128-Hz vibration tuning forks. Distal muscle strength (finger spread, great toe extension, ankle dorsiflexion) and deep tendon reflexes (biceps brachii, quadriceps femoris, and Achilles) were also assessed bilaterally. Polyneuropathy was defined as the presence of motor and/or sensation signs and paresthetic symptoms having a symmetric glove and/or stock distribution.[12] In order to obtain a grading of polyneuropathy, the SW testing and the 128-Hz tuning fork testing were scored from 0 to 2 points. In particular, the 10-g SW filament was tested on the plantar surface of the hallux and centrally at the heel. The ability to sense the SW monofilament correctly in 6 trials at both locations was defined as normal, scoring 0 points; the inability to sense the SW monofilament correctly in 1 of 6 trials was defined as mildly disturbed (score 1 point); and the inability to sense the SW monofilament correctly more than 1 time was defined as disturbed and scored 2 points. The vibrating tuning fork was put on the dorsum of the interphalangeal joint of the right hallux, and, when nothing was felt, the score was 2 points. When something was felt, the still-vibrating tuning fork was immediately placed at the dorsal wrist. When it was felt the same at that location, the score was 0 points; when it was felt stronger, the score was 1 point.[13]

Statistical Analysis

In patients with type 2 diabetes and in controls, general characteristics, laboratory data, presence and grading of polyneuropathy, and occurrence of RLS were compared using Student *t*-test for independent samples for continuous variables and by means of contingency tables and χ^2 test for nominal variables. The association between type 2 diabetes and RLS was evaluated by a multiple logistic regression model.

In diabetic patients and controls affected by RLS, metabolic parameters and characteristics of RLS were analyzed. To investigate the risk factors for RLS in the diabetic population, we divided the patients with type 2 diabetes in 2 groups—those affected by RLS (diabetic RLS$^+$) and those without RLS (diabetic RLS$^-$)—and we compared the 2 groups for general characteristics, metabolic parameters, medical history, use of medications, and presence and grading of polyneuropathy using an univariate statistical analysis (Student *t*-test for continuous variables and χ^2 test or likelihood ratio for nominal variables). We controlled our results using a multiple logistic regression model.

Data are displayed in tables as means and standard deviations (SD), if not otherwise specified. Odds ratios (OR) were computed using logistic regression. A P value < 0.05 was considered statistically significant. Statistical analysis was carried out using the SPSS 9.0 software (SPSS, Inc., Chicago, Ill).

RESULTS

General Characteristics

General characteristics of the diabetic patients and of the nondiabetic controls, with and without RLS, are reported in Table

Table 1—General Characteristics of the Diabetic Patients (All Subjects, RLS⁺ and RLS⁻) and of the Nondiabetic Controls (All Subjects, RLS⁺ and RLS⁻)

	Diabetic patients (n = 124)			Controls (n = 87)			P Value
	All subjects	RLS⁺ n = 22	RLS⁻ n = 102	All subjects	RLS⁺ n = 5	RLS⁻ n = 82	
Age, y	65.1 ± 8.6	64.2 ± 9.4	65.3 ± 8.5	67.8 ± 13.3	72.4 ± 7.4	67.5 ± 9.5	0.1
Men, %	64	36	70	53	0	56	0.1
Alcohol consumption, %	49	41	51	63	40	65	0.06
Coffee consumption > 3 cups/d, %	31	28	32	37	20	38	0.2
Current or former use of tobacco, %	52	50	53	45	60	44	0.2
BMI, kg/m²	28.8 ± 4.6	30.0 ± 4.2	28.6 ± 4.7	26.0 ± 3.6	24.5 ± 4.2	26.1 ± 3.6	0.001
Hemoglobin, g/dL	14.1 ± 1.0	13.7 ± 1.3	14.1 ± 0.9	13.7 ± 1.4	13.6 ± 1.5	13.7 ± 1.4	0.3
Creatinine, mg/dL	0.89 ± 0.2	0.85 ± 0.1	0.90 ± 0.1	0.87 ± 0.2	0.82 ± 0.2	0.87 ± 0.2	0.5
Total cholesterol, mg/dL	214.9 ± 46.2	205.2 ± 47.6	217.0 ± 46.2	204.8 ± 28.9	198.5 ± 14.0	205.2 ± 29.6	0.1
Triglycerides, mg/dL	163.7 ± 79.3	158.4 ± 69.7	164.9 ± 82.0	124.5 ± 43.5	136.2 ± 36.2	123.6 ± 44.2	0.002

Data are presented as mean ± SD unless otherwise indicated. P Values reported in the table refer to comparison between all patients with type 2 diabetes and all controls. Comparing restless legs syndrome positive (RLS⁺) and RLS negative (RLS⁻) groups, the only variable significantly different was sex, both in patients with type 2 diabetes (P < 0.003) and in controls (P < 0.02). Laboratory data were collected from all diabetic patients, expect 2 subjects affected by RLS, and from all controls. BMI refers to body mass index.

1. The only differences were body mass index and levels of triglycerides, which were significantly higher among diabetic patients. In patients with type 2 diabetes, the mean duration of the endocrine disease was 12.3 ± 9.9 years. Eighty-three percent of diabetic patients had a value of HbA$_{1c}$ < 9% (good or sufficient level) and only 21% of the patients were being treated with insulin. Most of the patients controlled their endocrine disorder with diet (8%), oral medications (22.6%), or diet plus oral medications (48.4%). Microvascular complications were reported by 33% of diabetic subjects, whereas macrovascular complications were less frequent (21%). Data regarding presence and grading of polyneuropathy in diabetic patients and controls, with and without RLS, are reported in Table 2.

RLS in Diabetic Patients and in Controls

Twenty-two patients with type 2 diabetes (17.7%) and 5 controls (5.5%), 3 of whom had pituitary and 2 with adrenal gland disorders, were diagnosed as affected by RLS (P < 0.01). This association was confirmed by a multivariate analysis that included as confounding variables age, sex, body mass index, triglycerides, and presence of polyneuropathy (see Table 3). The metabolic parameters of RLS patients did not differ between diabetic subjects and controls, although a trend toward significance was observed for TSH and FT3 (see Table 4). A large proportion of diabetics (37%) and controls (38%) were not able to verify the presence or absence of RLS symptoms in first-degree relatives. Six percent of patients with type 2 diabetes and 5% of controls reported having a first-degree relative affected by RLS. Among 22 diabetic subjects with RLS, only 6 (27%) reported a positive family history of the sleep disorder, whereas a larger but not significant percentage was observed in controls affected by RLS (40%). The age of onset of RLS was almost similar in diabetic patients and controls (60.0 ± 8.9 years vs 63.4 ± 7.6 years, respectively). All but 3 diabetic patients reported that RLS symptoms appeared after the onset of type 2 diabetes, and the mean interval between the onsets of the 2 disorders was 17.8 ± 8.7 years. RLS complaints were commonly reported as *deep* (86% of patients affected by type 2 diabetes and 100% of controls) and usually described as *urge to move* (68% of diabetic patients and 100% of controls). Only the 6 patients with clinical evidence of diabetic polyneuropathy reported their symptoms with other terms: 3 as *pain*, 2 as *electric*, and 1 as *burning*. The mean IRLS score was similar in diabetic patients and controls (14.9 ± 5.5 vs 18.0 ± 3.4, respectively). None of the RLS patients (both diabetics and controls) had ever taken specific drugs for the sensorimotor disorder. Three patients affected

Table 2—Presence and Grading of Polyneuropathy, Based on Semmes-Weinstein and on 128-Hz Tuning Fork Testing, in Diabetic Patients (All Subjects, RLS⁺ and RLS⁻) and in Nondiabetic Controls (All Subjects, RLS⁺ and RLS⁻)

	Diabetic patients (n = 124)			Controls (n = 87)			P Value
	All subjects	RLS⁺ n = 22	RLS⁻ n = 102	All subjects	RLS⁺ n = 5	RLS⁻ n = 82	
Presence of polyneuropathy, %	13	27	9	3	20	3	0.02
Score at SW testing	1.5 ± 0.5	1.7 ± 0.5	1.4 ± 0.5	1.3 ± 0.6	2.0 ± 0	1.5 ± 0.7	0.7
Score at tuning fork testing	1.4 ± 0.5	1.7 ± 0.5	1.3 ± 0.5	1.7 ± 0.6	2.0 ± 0	1.5 ± 0.7	0.6

Data are presented as mean ± SD unless otherwise indicated. P Values reported in the table refer to comparison between all patients with type 2 diabetes and all controls. Comparing restless legs syndrome positive (RLS⁺) and RLS negative (RLS⁻) groups, the only variable significantly different was polyneuropathy in type 2 diabetic patients (P < 0.02). No significant differences were observed between RLS⁺ and RLS⁻ controls. SW refers to Semmes-Weinstein.

Table 3—Odds Ratios (95% Confidence Intervals) for Restless Legs Syndrome in Patients With Type 2 Diabetes

Subjects	Model 1 Unadjusted	Model 2 Adjusted for age, sex, BMI and triglycerides	Model 3 Adjusted for the variables in model 2 plus presence of polyneuropathy
Controls	1.00	1.00	1.00
Diabetic patients	3.53 (1.28-9.74)	4.31 (1.06-17.47)	4.65 (1.07-20.17)

Odds ratio for the presence of restless legs syndrome, obtained from multiple logistic regression models using controls as the reference category. BMI refers to body mass index.

by type 2 diabetes were using benzodiazepines long-term to treat their anxiety symptoms.

Diabetic Patients with RLS (RLS⁺) Versus Diabetic Patients Without RLS (RLS⁻)

A significantly higher prevalence of women was found in the diabetic RLS⁺ than in the diabetic RLS⁻ group (64% vs 30%; P < 0.003), whereas the other variables included in the table of general characteristics did not differ (see Table 1). Comparing the diabetic RLS⁺ with the diabetic RLS⁻ groups, levels of HbA_{1c} (8.1 ± 1.4% vs 7.7 ± 1.4%) and ferritin (128.7 ± 75.5 mg/dL vs 118.6 ± 97.2 mg/dL; P = 0.70) were similar. The number of patients with a history of anemia with iron deficiency, hypothyroidism, uremia, and rheumatoid arthritis and those using antidepressants or antipsychotics was similar in the diabetic RLS⁺ and diabetic RLS⁻ groups. Presence and grading of polyneuropathy in diabetic RLS⁺ and RLS⁻ patients are reported in Table 2. The multivariate analysis—including age, sex, HbA_{1c}, creatinine, ferritin, duration of the endocrine disease, and use of antidepressants or antipsychotics as confounding factors—confirmed that diabetic peripheral neuropathy was an independent risk factor for RLS in diabetic patients (OR, 7.88; 95% confidence intervals, 1.34-46.28; P < 0.02), while the independent effect of sex was lost (OR, 1.64; 95% confidence intervals, 0.40-6.68; P = 0.5).

DISCUSSION

To our knowledge, this is the first controlled study confirming a significant association between RLS and type 2 diabetes. The prevalence of RLS in our diabetic patients (17.7%) was significantly higher than that reported in the general population, ranging from 5% to 10%,[14] whereas it was slightly lower with respect to previous studies carried out in subjects with type 2 diabetes. One such study had a sample size insufficient to demonstrate a significant association,[6] and the other was not a case-control study.[7]

Iron deficiency is a well-known condition correlated with several forms of symptomatic RLS,[1,3,15] but, in the diabetic population, RLS seems to be independent from the iron status of patients.[6] Our data are in agreement with previous results and confirm the lack of association between RLS and iron status in diabetic patients. Alternatively, Skomro et al[6] suggested that the presence of diabetic polyneuropathy could be responsible for the increased prevalence of RLS in patients with type 2 diabetes. The present study confirms the role of polyneuropathy as a risk factor for RLS in diabetic patients. However, our multivariate analysis showed that type 2 diabetes remains an independent risk factor for RLS even after adjusting for the presence of polyneuropathy. Therefore, polyneuropathy may not be the only cause of the increased prevalence of RLS in diabetic patients. If so, a central nervous system dysfunction may be suggested. This view could be supported by the findings of Gallego et al, who showed that the dopamine content of diabetic rats was reduced in several areas of the central nervous system, including striatum and midbrain, 2 regions important for RLS circuitry.[16] Although caution must be exerted in drawing conclusions, since this study was performed on an animal model of diabetes and similar data on humans are lacking, we wonder if the midbrain lesions observed by Gallego et al in diabetic rats may be responsible for functional alterations in the dopaminergic cell group A11 of the midbrain. In fact, in rats, specific lesions in A11 are able to lead to a general hyperactive state, evaluated as standing episodes and total standing time. This behavior, although not specific, is consistent with what would be expected in an animal model of RLS and is decreased after dopaminergic treatment.[17] A11 cells give origin to the major dopaminergic pathways projecting into the dorsal horns of the spinal cord, apparently modulating the nociceptive afferents.[18,19] Based on these considerations, we hypothesize that RLS in patients affected by type 2 diabetes could be due to the concurrence of a decreased inhibitory dopaminergic control on the dorsal horns of the spinal gray matter[18,19] with the excitatory nociceptive inputs due to the peripheral neuropathy.[20] Further clinical experimental studies are required to verify this hypothesis.

Our diabetic patients commonly described RLS symptoms using the term *urge to move*, but only patients with clinical signs of polyneuropathy described their disturbances as *pain, electric,* or *burning*, in accordance with previous results by Winkelmann et al in patients with sporadic RLS and electrophysiologic signs of peripheral nerve damage.[21]

In our diabetic population, RLS characteristics (frequency of positive family history of RLS lower than that known for primary RLS, late age of onset of RLS, and antecedence of type 2 diabe-

Table 4—Metabolic Parameters In Diabetic Patients and in Nondiabetic Controls Affected By Restless Legs Syndrome

Parameter	Diabetic patients (n = 20)	Controls (n = 5)	P Value
Hemoglobin, g/dL	13.7 ± 1.3	13.6 ± 1.5	0.8
Creatinine, mg/dL	0.85 ± 0.1	0.82 ± 0.2	0.6
Ferritin, ng/mL	128.7 ± 75.5	107.7 ± 38.9	0.4
Folate, ng/mL	6.4 ± 3.7	4.6 ± 2	0.1
Vitamin B12, ρg/mL	468.0 ± 146.4	404.0 ± 250.7	0.6
TSH, uUI/mL	2.1 ± 1.2	1.2 ± 0.8	0.07
fT3, ρg/mL	2.9 ± 0.4	3.4 ± 0.8	0.06
fT4, ρg/mL	12.2 ± 1.6	14.2 ± 2.5	0.1

Data are presented as mean ± SD.

tes onset to RLS onset) suggest that the sleep disorder should be considered as symptomatic. In fact, RLS appeared as a long-term complication of diabetes, many years after the onset of the endocrine disease.

Different from the score of patients with the uremic form of RLS,[22] in our subjects, the IRLS score was only moderate (14.9). A low severity of RLS and a focus on polyneuropathy may account for the fact that our endocrinologists did not detect and treat RLS.

In patients affected by RLS, the unpleasant sensations may lead to a severe difficulty in initiating and maintaining sleep, disrupting sleep architecture and causing an important sleep curtailment. A chronic sleep debt, as observed in RLS patients, has been shown to be a predictor of mortality.[23] Patients with restless legs appear to have a significantly higher risk of ischemic stroke than do subjects without this sleep disorder.[24] The association between RLS and cerebrovascular diseases could be due to the effects of a prolonged sleep loss in increasing the probability of developing hypertension and diabetes,[25-28] which are 2 known predictors of vascular diseases. Therefore, in the diabetic population, RLS and diabetes can interact in a vicious circle. Hence, RLS symptoms should be adequately treated in order to help with the management of the endocrine disease and, consequently, to reduce the risks of mortality caused by vascular diseases.

A limitation of our study needs to be discussed. In fact, although recommended for epidemiologic studies,[12] diagnosis of polyneuropathy was made using only a clinical approach. The simultaneous presence of neuropathic signs and symptoms with distal symmetric distribution has a good sensitivity,[12] but, nevertheless, some diabetic patients with subclinical polyneuropathy might have been missed. However, even a neurophysiologic exam cannot be totally sensitive. In fact, it is not able to diagnose the "pure" small-fiber neuropathy, which can be ruled out only by skin biopsy, although this approach is not practical for use in a large sample of subjects.

CONCLUSIONS

Our study demonstrates a clear association between RLS and type 2 diabetes. It also shows that polyneuropathy is an independent risk factor for the appearance of RLS in patients with diabetes. Awareness regarding correct RLS identification and treatment in this specific population is recommended. In addition, detailed results of the prevalence of diabetes in future RLS studies should be reported.

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