

Research Article

Restless leg syndrome as co-morbidity in type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes is a global epidemic with India estimated to have the highest prevalence of 79.4 million by 2030. RLS is a common yet undiagnosed comorbidity causing significant distress. We aimed to analyze association between restless legs syndrome (RLS) and type 2 diabetes.

Methods: One hundred fifty six type 2 diabetes mellitus (T2DM) and eighty eight non-diabetic controls were assessed at Mahatma Gandhi Medical College & Hospital, Jaipur, India for RLS using the international RLS study group rating scale. Several patient clinical profiles along with laboratory parameters were compared in both groups. Diabetic polyneuropathy was evaluated for its role as risk factor in diabetic RLS subjects.

Results: RLS was diagnosed in 35 diabetic patients (22.44%) and in only 7 non diabetic controls (7.95%). RLS was independently associated with type 2 diabetes ($P < 0.04$). A clinical diagnosis of polyneuropathy was made in only 22.86% of diabetic patients with comorbid RLS. In multivariate logistic regression, polyneuropathy was the only variable associated with RLS in diabetics ($P < 0.03$). RLS manifested in diabetics after the diagnosis of diabetes was made.

Conclusions: An association between RLS and type 2 diabetes is established in Indian subpopulation. In diabetic patients, polyneuropathy is the main risk factor for RLS. But, polyneuropathy only partially explains the increased prevalence of RLS in type 2 diabetics.

Keywords: RLS, Type 2 diabetes, Polyneuropathy

INTRODUCTION

Restless leg syndrome (RLS) is a sleep disorder, with sensorimotor neurological symptoms. This includes an urge to move legs or other extremities during rest. This may be associated with unpleasant sensations relieved by movement. The revised international restless legs syndrome study group (IRLSSG) 2012, has described 5 essential clinical features to establish the diagnosis of RLS; (i) an urge to move the legs, usually but not always

accompanied or caused by uncomfortable and unpleasant sensations in the legs; (ii) these symptoms begin or worsen during periods of rest or inactivity such as lying or sitting; (iii) are partially or totally relieved by movement; and (iv) symptoms are worse in the evening or nighttime; (v) not solely accounted by other medical or behavior condition. A high level of suspicion of an association between T2DM and RLS stems from a common pathophysiological association of both with “polyneuropathic” degeneration.

Clinical conditions like iron deficiency, uremia, pregnancy, Polyneuropathy, and rheumatoid arthritis, have been associated with RLS, presenting as a secondary or symptomatic form.¹⁻⁵ There are still no rigorous studies investigating the association between type 2 diabetes mellitus and RLS in Indian subgroup which is projected to become “the diabetic capital of world”.

METHODS

Patient selection

In our study, 156 patients with type 2 diabetes, at Mahatma Gandhi Medical College & Hospital, Jaipur, India were recruited from September 2013 to April 2014. The control group consisted of 88 consecutive patients who were attending the OPD and were diagnosed with medical disorders other than diabetes. A formal written consent was taken from all patients. Subjects younger than 18 years of age were excluded from the study. Also, pregnant women were excluded from the study, because of expected high prevalence of RLS, which might act as a confounding factor. Other clinical conditions excluded were myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping, Parkinson disease; myelopathy; L4, L5, or S1 radiculopathy; and dialysis dependence.

General protocol

Patient's clinical profiles were reviewed and information was procured pertaining to demographic aspects, past medical history, and use of medications. Conditions favouring RLS (iron deficiency anaemia, hypothyroidism, rheumatoid arthritis and uremia) and drugs which worsen RLS symptoms (antidepressants or antipsychotics) or improve RLS symptoms (benzodiazepines, dopaminergic agents, and anticonvulsants like carbamazepine, oxcarbazepine, gabapentin and valproic acid). Diabetic profile of patients was inquired for duration, complications (subdivided into micro-vascular, 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 for comorbid medical condition.

RLS protocol

Both diabetic patients and controls were screened using revised international restless legs syndrome study group diagnostic criteria 2012.⁶ Only subjects who fulfilled all criteria were considered affected by RLS and were further evaluated with 10 additional questions to assess RLS severity, using the international restless legs syndrome study group rating scale (IRLS).⁷ RLS symptoms in first-degree relatives was enquired for all diabetic patients and in controls. Moreover, diabetic patients and controls with RLS were investigated

concerning, age of RLS symptom onset, localization (deep or superficial) and description of RLS symptoms (choosing between pain, burning, urge to move, electric, pulling, or other).⁸

Laboratory data

Among the various laboratory parameters evaluated were blood samples (complete blood count, glucose, total cholesterol, triglycerides, and creatinine) in all patients and controls, glycosylated hemoglobin (HbA1c) in all T2DM subjects. All patients diagnosed with RLS were evaluated for serum folate, vitamin B₁₂, thyroid profile. Ferritin was obtained in all diabetic patients and in controls affected by RLS.

Evaluation of polyneuropathy

A thorough examination for distal symmetric polyneuropathy (examination of sensory system, distal muscle strength, deep tendon reflexes etc.) both in diabetic patients and in controls. Semmes Weinstein (SW) filaments and 128-Hz vibration tuning forks were used to assess distal sensory function. Polyneuropathy was defined as the presence of motor and/or sensation signs and paresthetic symptoms having a symmetric glove and/or stock distribution.⁹

Polyneuropathy was graded from 0 to 2 points (SW testing and 128-Hz tuning fork). The 10-g SW filament was tested on plantar surface of hallux and center of the heel. Sensation of the monofilament in 6 trials at both locations was defined as normal, scoring 0 points; the inability to sense in 1 of 6 trials was defined as mildly disturbed (score 1 point); and more than 1 time was defined as disturbed and scored 2 points. The vibrating tuning fork was put on dorsum of the interphalangeal joint of the right hallux, and, for “no sensation” score given 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.¹

Statistical analysis

Student t-test was used for independent samples and χ^2 test for nominal variables. Multiple logistic regression models were used. 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 12.0 software (SPSS, Inc., Chicago, Ill).

RESULTS

Table 1 summarizes general characteristics of the diabetic patients and non-diabetic controls, with and without RLS. Body mass index and levels of triglycerides, were significantly higher among diabetics. The mean duration

of type 2 diabetes, was 14.6 ± 8.2 years. 73.08% of diabetics had a value of HbA1c $<9\%$ (good or sufficient level) and only 17.9% of the patients were using insulin as therapy. Other therapeutic measures used were, diet

(8.97%), oral medications (26.28%) and diet plus oral medications (46.79%). 28.21% diabetics presented with microvascular and 19.23% with macrovascular complications.

Table 1: General characteristics of diabetic and non-diabetic subjects.

	Diabetics (N=156)			Controls (N=88)			P value
	ALL	RLS	NO RLS	ALL	RLS	NO RLS	
Age, years	64.6 ± 7.2	63.4 ± 8.6	64.1 ± 8.2	66.4 ± 12.8	70.2 ± 6.8	66.2 ± 9.3	0.1
Men (%)	54	34.2	69.42	54.55	0	59.26	0.12
Alcohol (%)	41.03	37.14	42.15	62	38.71	61.29	0.08
Tobacco % (Current/Past)	52.56	51.43	52.89	44.31	28.57	45.68	0.22
BMI Kg/m ²	28.6 ± 4.2	29.7 ± 4.4	28.1 ± 4.5	26.2 ± 3.2	24.1 ± 4.4	26.5 ± 3.4	0.001*
Haemoglobin g/dl	14.8 ± 1.2	14.1 ± 1.6	14.3 ± 0.9	12.9 ± 1.6	13.1 ± 1.6	13.4 ± 1.5	0.3
Creatinine mg/dl	0.88 ± 0.4	0.85 ± 0.2	0.92 ± 0.1	0.86 ± 0.2	0.84 ± 0.2	0.86 ± 0.2	0.6
Total Cholesterol mg/dl	216 ± 44.6	196.4 ± 43.4	201.7 ± 45.2	192.8 ± 26.7	188.9 ± 16.1	194.4 ± 29.4	0.1
Triglyceride, mg/dl	172.9 ± 77.5	162.4 ± 69.9	174.7 ± 80.4	128.9 ± 44.7	138.2 ± 38.4	125.6 ± 42.2	0.002*

* $p < 0.05$; Data are presented as mean \pm SD. P Values refer to comparison between patients with type 2 diabetes and controls; Comparing restless legs syndrome positive (RLS) and No RLS groups.

Table 2: Polyneuropathy: presence and grading.

	Diabetics (N=156)			Controls (N=88)			P value
	ALL	RLS	NO RLS	ALL	RLS	NO RLS	
Presence of polyneuropathy %	15.38	31.43	11.57	6.68	20	6.1	0.03*
Score of SW testing	1.6 ± 0.5	1.8 ± 0.5	1.5 ± 0.5	1.4 ± 0.6	2.0 ± 0.5	1.6 ± 0.7	0.9
Score at tuning fork testing	1.5 ± 0.5	1.8 ± 0.5	1.4 ± 0.5	1.8 ± 0.6	2.0 ± 0.5	1.6 ± 0.7	0.8

* $P < 0.05$; Data are presented as mean \pm SD. P Values refer to comparison between patients with type 2 diabetes and controls. Comparing restless legs syndrome positive (RLS) & No RLS groups. SW refers to Semmes-Weinstein.

Table 3: Parameters in diabetic and non-diabetic controls in subjects affected by restless leg syndrome.

Parameter	Diabetics (N=35)	Controls (N=7)	P value
Hemoglobin, g/dl	11.7 ± 1.4	11.9 ± 1.5	0.8
Creatinine, mg/dl	0.83 ± 0.2	0.8 ± 0.2	0.6
Ferritin, ng/ml	122.8 ± 70.5	104.7 ± 36.8	0.5
Folate, ng/ml	6.6 ± 3.2	4.8 ± 2.2	0.2
Vitamin B12, pg/ml	472 ± 142.4	412 ± 238.7	0.6
TSH, bUI/ml	2.3 ± 1.4	1.4 ± 0.8	0.09
fT3, pg/ml	2.7 ± 0.6	3.2 ± 0.6	0.06
fT4, pg/ml	12.6 ± 1.8	14.6 ± 2.8	0.1

Thirty five patients with type 2 diabetes (22.44%) and 7 controls (7.95%), were diagnosed as affected by RLS ($P < 0.01$). This association was reintegrated in a multivariate analysis including confounding variables age, sex, triglycerides, body mass index and polyneuropathy. The metabolic parameters of RLS patients were similar in both diabetic and control group, although a slight trend toward significance was seen with TSH and FT3 (see Table 3). The age of onset of RLS

symptoms was similar in both diabetics and control study groups (62.6 ± 7.7 years versus 63.2 ± 6.4 years, respectively). All but 7 diabetic patients reported RLS symptoms to have appeared after type 2 diabetes onset, and the mean interval between the onsets of T2DM & RLS was 18.2 ± 6.5 years. Most commonly RLS symptoms were described as deep (76.28% of T2DM and 100% of control subjects) and as an urge to move lower limbs (65.38% of T2DM and 100% of control subjects). Only the 8 subjects with diabetic polyneuropathy reported their symptoms differently (4 pain, 2 electric, and 2 burning). Mean IRLS score was similar in diabetic patients and controls (16.2 ± 6.2 versus 18.8 ± 4.4 , respectively). No RLS patient from diabetic or control group gave history of intake of any specific drugs for the sensorimotor disorder. Six T2DM subjects were using long-term benzodiazepines for anxiety symptoms.

- A significant higher number of females were found among diabetic patients with RLS than in the diabetics with no RLS symptoms (65.71% versus 30.58%; $P < 0.002$). Diabetics with RLS as a group were similar to diabetic without RLS, in reference to, levels of HbA1c and ferritin, history of anemia with

iron deficiency, uremia, hypothyroidism, rheumatoid arthritis and use of antidepressants or antipsychotic medication. Presence and grading of polyneuropathy in diabetic RLS+ and RLS- patients are reported in Table 2. The multivariate analysis confirmed that diabetic peripheral neuropathy was an independent risk factor for RLS in diabetic patients (OR, 6.98; 95% confidence intervals, $P < 0.02$).

DISCUSSION

In our study the prevalence of RLS in diabetic patients (22.44%) was significantly higher than that reported in general population (5% - 10%) as suggested by Zucconi M et al.¹¹ Alternatively, it was slightly lower than few previous studies on type 2 diabetics. But such studies suffered various drawbacks, ranging from insufficient sample size for demonstrating a significant association¹² and another which was not a case-control study.^{12,13} Iron deficiency has a proven correlation with RLS, but, in Indian diabetics, RLS seems to be independent from the iron status of patients.^{1,3,14} 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 suggested that diabetic polyneuropathy could be held responsible for an increased prevalence of RLS in patients with type 2 diabetes.¹² Our study confirms the role of polyneuropathy as a risk factor for RLS in diabetic patients. However, multivariate analysis in our study showed that type 2 diabetes is an independent risk factor for RLS even after adjusting for the presence of polyneuropathy. Hence, the high prevalence of RLS in diabetics may not be solely because of polyneuropathy. Also, a central nervous system dysfunction has been suggested by Gallego et al, who showed reduced dopamine content in striatum and midbrain regions, both of which are important for RLS circuitry.¹⁵ But, similar studies in humans are lacking. 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 its hypothesized that in rats functional alterations in the dopaminergic cell group A11 of the midbrain, cause general hyper-active state and is decreased after dopaminergic treatment.¹⁶ A11 cells supply major dopaminergic pathways projecting in the dorsal horns of the spinal cord, supposedly modulating the nociceptive afferents.^{17,18} Based on these observations, we suggest that type 2 diabetics affected by RLS may be due to a decreased inhibitory dopaminergic control on the dorsal horns of the spinal gray matter and the excitatory nociceptive inputs may be due to the peripheral neuropathy.¹⁷⁻¹⁹ Further clinical research is needed in this direction.

Diabetics in our study frequently described RLS symptoms as “urge to move”, but only those with polyneuropathy described their symptoms as painful,

burning or electric, as also suggested by Winkelmann et al.²⁰ In diabetics RLS appeared as a long-term complication of diabetes, many years after T2DM onset. RLS causes unpleasant sensations causing severe difficulty in initiating and maintaining sleep in subjects, disrupting sleep. Chronic sleep deficiency, as seen in RLS patients, is a predictor of mortality.²²

Patients with restless legs appear to have a significantly higher risk of ischemic stroke which has been postulated to be caused by prolonged sleep loss, increasing the probability of developing hypertension and diabetes leading to vascular pathology. Hence RLS and T2DM share a bidirectional relationship, and evaluation of RLS in diabetic patients may give mortality benefit in long chronic disease course.²³⁻²⁷

A limitation of our study was using clinical criteria for diagnosing “polyneuropathy”. Hence, we might have missed the subclinical polyneuropathy cases which can only be diagnosed using a neurophysiologic exam, and “pure” small-fiber neuropathy cases, which can be ruled out only by skin biopsy, which is impractical in such large samples.

CONCLUSION

This study suggests an association between RLS & T2DM subjects. Also it proves polyneuropathy as an independent risk factor for RLS presentation in diabetics. Proper, early diagnosis and treatment of RLS may go a long way in reducing morbidity and probably mortality in diabetic patients.

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Ethical approval: The study was approved by the institutional ethics committee

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