Journal of the Neurological Sciences 287 (2009) 60–63

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Role of the Oral Glucose Tolerance Test (OGTT) in the idiopathic restless legs syndrome

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ARTICLE INFO

Article history:
Received 10 April 2009
Received in revised form 4 September 2009
Accepted 8 September 2009
Available online 26 September 2009

Keywords:
Restless legs syndrome
Restless legs syndrome and prediabetes
Small fibres neuropathy
2h-OGTT

ABSTRACT

Background: Restless legs syndrome (RLS) is a sensorimotor disorder characterised by a distressing urge to move the legs. Several clinical conditions have been associated with RLS, such as iron deficiency, uraemia, pregnancy, polyneuropathy and Diabetes Mellitus (DM). However the causes remain unknown in about 70–80% of cases.
Objective: To evaluate the role of glucose metabolism abnormalities in idiopathic RLS.
Methods: We enrolled 132 consecutive patients with idiopathic RLS associated with normal fasting glycaemia and 128 control subjects. We evaluated glucose and insulin levels after a 2-h oral glucose tolerance test (2h-OGTT) in patients and control subjects. In addition we determined Insulin Resistance (IR) by Homa-Index.
Results: After 2h-OGTT, the prevalence of glucose metabolism abnormalities was significantly higher in patients with RLS than in controls ($P = .002$). Impaired Glucose Tolerance (IGT) was found in 54 (41%) patients and in 23 (18%) controls, while a new-diagnosed DM (NDDM) was found in 25 (19%) patients and in 8 (6%) controls. The IR showed no significant differences between patients and controls.
Conclusions: Our study suggests that IGT (prediabetes) is frequently associated with idiopathic RLS. We propose to perform a 2h-OGTT in idiopathic RLS patients with normal fasting glycaemia.
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1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a distressing urge to move the legs. The diagnosis of RLS is based on the presence of four essential criteria, with the addition of three supportive clinical features, developed by the International RLS Study Group (IRLSSG) in 2003 [1]. RLS is divided into a primary and a secondary form. Primary or idiopathic RLS is diagnosed when clinical conditions responsible for secondary forms are excluded by laboratory, neurological, neurophysiological and neuroradiological examinations; it accounts for about 70–80% of all RLS cases [2]. A large part of idiopathic RLS is represented by hereditary forms [3]. As idiopathic and secondary RLS show a positive response to dopaminergic treatment, many physicians do not look into possible causative conditions [4]. Thus, we suppose that some of the sporadic-idiopathic RLS may be secondary or cryptogenic. Among symptomatic forms, several conditions are associated with RLS, such as iron deficiency [5], uraemia [6], pregnancy [7], polyneuropathy [8] and type 2 diabetes mellitus (DM2) [9]. Prediabetes is defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) following a 2-h oral glucose tolerance test (2h-OGTT).

In the present study, performed in our country (Calabria, Southern Italy), we assessed glucose metabolism abnormalities in 132 patients with idiopathic RLS and normal fasting glycaemia.

2. Methods

2.1. Patients and ethical committee approval

The study was approved by the Ethical Committee of "S. Giovanni di Dio" Hospital, Crotone, Italy. All patients gave their consent, in accordance with the official standards of the 1964 declaration of Helsinki, local laws and regulations. We studied prospectively 132 patients with idiopathic RLS and normal fasting glycaemia, and 128 control subjects, between February 2005 and January 2009. All patients satisfied the essential criteria proposed by the IRLSSG for the diagnosis of RLS. Exclusion criteria were: a. family history of neuropathy; onset before 50 years of age, positive family history for RLS b. distal symmetric neuropathy c. toxic or alcohol overuse, disthyroidism, autoimmune and

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doi:10.1016/j.jns.2009.09.008

infective conditions d. abnormal results on blood tests including electrolytes, blood glucose, HbA_{1c}, renal function, liver function, complete blood cells count, B12 level, serum protein electrophoresis, iron level e. pregnancy; f. extrapyramidal disorders; g. medullary diseases [10].

We enrolled as controls, normal subjects coming from the same geographic area, ethnic background and with similar life style of patients. Control subjects did not have clinical evidence of RLS and/or systemic disorder, DM, uremia and iron illness. Moreover, for all patients we considered the subjective description of RLS symptoms that were referred such as "urge to move the legs, burning sensation, pulling and pain sensation".

2.2. Evaluation

Patients were evaluated by an endocrinologist and a neurologist expert in peripheral nervous system disorders. After a first-level check-up, all patients underwent the following tests: Magnetic Resonance Imaging (MRI) with gadolinium of the lumbar-sacral tract; electromyographic (EMG) study, including at least compound muscle action potentials (CMAPs), conduction velocities (CV) and distal latencies of peroneal nerves, sensory action potentials (SAPs) of sural nerves, late responses (F wave and H-reflex) of tibial nerves**.** Skin biopsy was performed on all patients to exclude small fibres neuropathies [11]. Skin samples were obtained from the distal region of the leg, 10 cm above the lateral malleolus, within the sural nerve territory. The linear density of intraepidermal nerve fibre (IENF) quantification (IENF/mm) was calculated according to the guidelines of the European Federation of the Neurological Societies [12]. Recorded medical data for both patients and controls included: anamnestic data (dietary habits, life style), demographic informations (age, sex), Body Mass Index (BMI), waist circumference, glucose and insulin values at fast and after 2 h-OGTT, serum HbA_{1c}, cholesterol, triglyceride, iron and ureic levels. Procedure for the 2 h-OGTT required fasting after mid-night, obtaining a baseline fasting glucose level, and administration of the oral glucose load within a 5-minute period. Blood specimens to determine plasma glucose and insulin levels were subsequently drawn at 120 min, timed from the beginning of the glucose load. Insulin resistance (IR) was calculated by the homeostasis model assessment (HOMA) formula [13]. Patients and controls were established as having IGT if the 120-minute venous plasma glucose value fell between 140 and 200 mg/dL. Criteria for new-onset DM were fasting plasma glucose level higher than 126 mg/dL or 120-minute venous plasma glucose level higher than 200 mg/dL on the 2h-OGTT [14].

2.3. Data analysis

Data were expressed as mean ± SD. Patients were compared to controls with respect to variables representing their current status and potentially, the aetiology of the condition. For categorical variables, this was performed by comparing distributions using χ^2 tests and for calculated variables by comparing means using t tests with correct test of the normal assumption required. When they were not satisfied due to skewed data distributions, logarithmic transformations were used. Finally, to assess and allow for discrepancies among the clinical characteristics in the group comparisons and to assess the relative significance of potential aetiological variables, logistic regression was used. In all cases, a P value of 0.05 was considered statistically significant.

3. Results

3.1. Demographic features

During a period of four years, from 2005 to 2009, we recruited prospectively 132 (86 women and 46 men) patients, with idiopathic RLS. Mean age in the patients group was significantly higher than in controls group (56.4 ± 5.9 vs 50.5 ± 6.8 years; $P = .002$). All subsequent statistical comparisons of the two groups took age into account. The mean duration of symptoms was 32.9 ± 9.4 months (Table 1).

3.2. Impaired glucose tolerance and insulin resistance

The mean fasting glucose value was 70 ± 10.1 mg/dl in patients group and 79 ± 6.8 mg/dl in controls group respectively ($P = 2.1$). Following 2 h-OGTT, we found glucose metabolism abnormality in 79 (60%) patients (54 with IGT and 25 with DM) and in 31 (24%) control subjects (23 with IGT and 8 with DM). After adjustment for age the difference between patients and controls was significant ($P < .001$). Prevalence of IR was similar in both groups after age-adjusted analysis ($P = .25$) (Fig. 1).

3.3. Clinical features

BMI, waist circumference, mean values for blood pressure, triglycerides, serum lipid, iron and uremic levels, after the adjustment for age, were not significantly different between patients and controls ($P = 1.9$). History of antidepressant or antipsychotics use was similar in patients and controls (patients vs controls: 15 vs 11; $P = 3.4$). Smoking use, defined as cumulative cigarettes/day, was significantly higher in patients than in controls (patients vs controls: 14.3 ± 4.1 vs 9.2 ± 2.6). However, after adjustment for age, this difference was not significant ($P = 1.7$). Waist circumference values showed a small but not significant increase in patients with RLS vs controls (81.5 ± 8.5 mg/dl vs 79.8 ± 5.8 cm; $P = .19$), after adjustment for age and antidepressant or antipsycotics use. RLS symptoms were referred as urge to move the legs in 66 patients, burning sensation in 34 patients, pulling in 20 patients and pain sensation in 12 patients. (Table 2).

3.4. Skin biopsy

Small fibre sensory neuropathy (SFN) was found in 69 (52%) patients, of whom 24 (18%) had DM, 40 (30%) had IGT and 5 (4%) had normal glucose metabolism (NGM). SFN prevalence was significantly higher in patients with abnormal glucose metabolism (RLS with Abnormal Glucose Metabolism vs RLS without Abnormal Glucose Metabolism: 48% vs 4%). No significant difference was found in the

Table 1
Features of 132 patients with "idiopathic restless legs syndrome" and 128 control subjects.

	Patients	Controls	*P*
Number of patients	132	128	2.5
Age; years	56.4 (5.9)	50.5 (6.8)	.002
Sex (m/f)	86/46	88/40	.32
Fasting glycaemia (mg/dl)	70 (10.1)	79 (6.8)	2.1
Fasting insulinemia (UI/ml)	12.3 (1.6)	13.4 (2.9)	2.1
Waist circumference (cm)	81.5 (8.5)	79.8 (5.8)	.19
BMI	23.1 (2.3)	22 (3.4)	1.6
HOMA-index	2 (0.6)	2.4 (0.5)	2.2
Triglycerides (mg/dl)	138 (19.2)	143 (9.1)	.12
Serum lipid (mg/dl)	124 (16.1)	135 (10.1)	.79
Iron level (mcg/dl)	95.4 (15.8)	99 (16.3)	1.2
Uraemic level (mg/dl)	38 (4.9)	42 (6.8)	.95
Smoking, (cigarettes/day)	14.3 (4.1)	9.2 (2.6)	1.7
Antipsychotic/antidepressant use	15/132	11/128	3.4
Systolic pressure; (mmHg)	117.7 (12)	119 (9.7)	.81
Diastolic pressure; (mmHg)	72.7 (6.9)	69 (9)	.79

Abbreviations: Body Max Index: BMI [Weight (kg)/height^2 (h^2]; HOMA Index: Basal Glucose Plasma (mg/dl) × Basal Insulin Plasma (UI/ml)/405; The differences between the proportions with Insulin Resistance ≥ 2.7 on the HOMA formula. Values are expressed as mean (SD) unless otherwise indicated. *P*-value was evaluated after adjustment for age and sex.

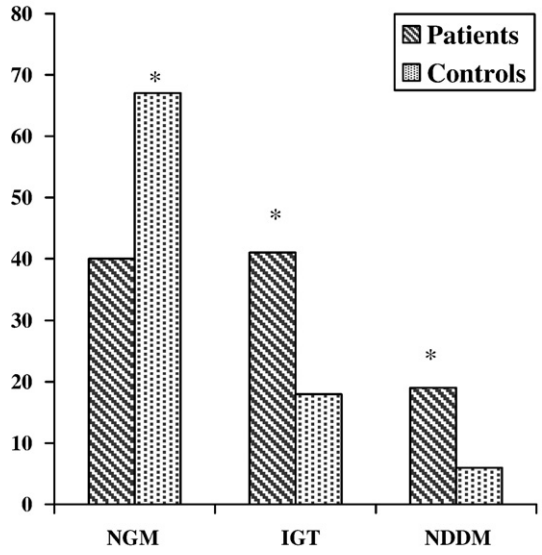

Fig. 1. Prevalence of abnormal glucose metabolism after a 2 h-OGTT test in 132 patients with idiopathic restless legs syndrome and 128 control subjects. *P*-value: <.001. Abbreviations: NGM, Normal Glucose Metabolism; IGT, Impaired Glucose Tolerance; NDDM, Newly Diagnosed Diabetes Mellitus.

subjective descriptions RLS symptoms between patients with and without SFN (Table 2).

4. Discussion

In this study, performed in our country (Calabria, Southern Italy) we investigated the prevalence of abnormal glucose metabolism (IGT and DM) by 2h-OGTT in patients with RLS of undetermined aetiology. Sixty percent of our patients following a 2h-OGTT showed abnormal glucose metabolism, of whom 41% having IGT and 19% DM. These percentages were significantly higher than those reported in our control subjects ($P<.001$). A decade of small epidemiology studies [15] offers evidence that early hyperglycaemia is sufficient to damage distal peripheral nerves. In fact, most of the clinical studies suggest that neuropathy is more common in patients with prediabetes, and that prediabetes is more frequent in patients with otherwise idiopathic neuropathy. As a matter of fact, a prospective study of 187 patients with idiopathic neuropathy found 45% of patients with IGT and a further 15% with previously unrecognized diabetes [16]. The association between RLS and DM2 is well documented. Skomro et al. found that RLS was more common (nearly double) in diabetic patients than in controls [9]. However the small size of their sample did not allow a statistical significance for the association. A recent cross-sectional study on DM2 patients reported a high prevalence of RLS (27%), but it had no control group [17]. Merlino et al. demonstrated in a case control study that the prevalence of RLS in DM2 is 17.7%, significantly higher than in controls [18]. RLS was found to be independently associated with DM2. Their findings confirmed that neuropathy is a risk factor for RLS development, but they suggested, on the basis of multivariate analysis, that neuropathy only partially explains the increased prevalence of RLS in diabetes. However, RLS in DM2 patients showed low incidence of family history and late onset, generally after diagnosis of diabetes, confirming the secondary nature of this RLS form. However, the relationship between RLS and prediabetes is controversial; previous retrospective studies already documented an association between RLS and IGT [19,20]. Besides, the authors suggested a small fibre involvement in RLS related with neuropathy. Indeed in diabetic neuropathy they recently showed that small fibre injury is present in association with IGT/IFG [20]. Summer et al. analyzing epidermal fibres on skin specimens, suggested that patients with IGT had less severe neuropathy with preferential small fibre involvement than patients with DM [15].

Table 2
RLS features in 132 patients with and without Small Fibre neuropathy.

	Number of patients	RLS + SFN *N*, (%)	RLS − SFN *N*, (%)	*P*
Urge to move the legs	66	34 (52)	32 (48)	2.1
Burning sensation	34	17 (50)	17 (50)	1
Pulling	20	11 (55)	9 (42)	1.3
Pain sensation	12	7 (58)	5 (42)	1.5

Abbreviations: SFN: small fibre neuropathy; RLS with SFN: RLS + SFN; RLS without SFN: RLS − SFN.

Our data documented a strong association between RLS and glucose metabolism abnormalities (IGT, DM) after 2h-OGTT, in patients with normal fasting glycaemia. A methodological limitation of our study was the control group: to obtain a convenient sample of control subjects, we recruited people matched for sex, geographic, ethnic background, dietary habits and life style; they were not matched for age. Nevertheless, after adjustment for this variable, there was no difference in waist circumference, HOMA-index, blood pressure, triglyceridemia, iron, uremic and serum lipid levels, smoking and antipsychotic use between RLS patients and controls, while the association between abnormal glucose metabolism and RLS remained strongly significant. This association could be explained in several ways. RLS may reflect the involvement of small sensory fibres in the form of hyperexcitable C-fibres [21]. Alternatively, abnormal thermal sensations may be produced by impaired central integration of informations from nociceptive and thermal channels, as suggested for paradoxical heat sensation produced by A-delta fibre deafferentation [22]. However, small fibre damage may not be the only cause involved in patients with RLS and abnormal glucose metabolism. A central nervous system dysfunction may be suggested. In fact, in diabetic rats the dopamine content was reduced in several areas of the central nervous system, including striatum and midbrain (dopaminergic cell group A11), two important regions for RLS circuitry [23]. A11 cells give origin to the major dopaminergic pathways projecting into the dorsal horns of the spinal cord, apparently modulating the nociceptive afferents [24]. In patients with abnormal glucose metabolism RLS could be due to the concurrence of a decreased inhibitory dopaminergic control on the dorsal horns of the spinal grey matter with excitatory nociceptive inputs due to the peripheral neuropathy [25].

This could be a valid explanation for a large part of patients who were positive for SFN at skin biopsy (RLS with abnormal glucose metabolism vs RLS without abnormal glucose metabolism: 48% vs 4%; $P<.001$). Nevertheless, in about 12% of our patients with RLS and abnormal glucose metabolism, skin biopsy was negative for SFN. This may be due to skin biopsy sensitivity of about 88% for SFN [26]; however, we could not exclude other possible causes of RLS in these patients. Besides, no differences were found in RLS features between subjects with and without SFN.

Finally, our data indicate that skin biopsy does not provide adjunctive informations in the assessment of pre-diabetic status; so, we propose to perform a 2h-OGTT in all patients with idiopathic RLS and normal fasting glycaemia, to evaluate an impaired glucose metabolism. Moreover, in these patients, an intensive treatment of prediabetes could be effective in the management of RLS [27,28]. Additional case-control studies matched for sex and age are needed before defining causal relationship between idiopathic RLS and prediabetes.

References

[1] American Academy of Sleep Medicine. International Classification of Sleep Disorders, 2nd edn (ICSD-2). Diagnostic and coding manual. American Academy of Sleep Medicine, Westchaster, IL 2006.
[2] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless Legs Syndrome diagnosis and epidemiology workshop at the national

institute of health in collaboration with members of the international Restless Legs Syndrome Study Group. RLS: Diagnostic criteria, special considerations and epidemiology, 4; 2003. p. 101–19.
[3] Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, Trenkwalder C. Clinical characteristics and frequency of the hereditary RLS in a population of 300 patients. Sleep 2000;23:597–602.
[4] Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology 2006;67:125–30.
[5] Okeeffe ST, Gavin K, Lavan JN. Iron status and Restless Legs Syndrome in the elderly. Age Ageing 1994;23:200–3.
[6] Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, Budai R. Restless legs syndrome in end stage renal disease. Sleep Med 2004;5:309–15.
[7] Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, Mollica G, Ferini-Strambi L, Granieri E. Restless legs syndrome and pregnancy. Neurology 2004;63:1065–9.
[8] Rutkove SB, Matheson JR, Logigian EL. Restless legs syndrome in patients with polyneuropathy. Muscle Nerve 1996;19:670–2.
[9] Skomro RP, Ludwig S, Salamon E, Kryger MH. Sleep complaints and restless legs syndrome in adult type 2 diabetes. Sleep Med 2001;2:417–22.
[10] Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, Mc Arthun JC. Subclinical sensory neuropathy in late-onset restless legs syndrome. Neurology 2000;55:115–21.
[11] Hoitsma E, Reulen JP, De Baets M, Drent M, Spaans F, Faber CG. Small fibre neuropathy: a common and important clinical disorder. J Neurol Sci 2004;227:119–30.
[12] Lauria G, Cornblath DR, Johansson O, McArthur JC, Mellgren SL, Nolano M, Rosenberg N, Sommer C. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol 2005;12:747–58.
[13] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
[14] Genuth S, Alberti KG, Bennett P. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;52:833–7.
[15] Summer C, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. Neurology 2003;60:108–11.
[16] Dyck PJ, Devies JL, Wilson DM, Service FJ, Melton III LJ, O'Brien PC. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study Cohort. Diabetes Care 1999;22:1479–86.
[17] Lopes LA, De MM LinsC, Adeodato VG, Quental DP, Debruin PFC, Montenegro RM, De Bruin VMS. Restless legs syndrome and quality of sleep in type 2 diabetes. Diabetes Care 2005;28:2633–6.
[18] Merlino G, Fratticci L, Valente M, Del Giudice A, Noacco C, Dolso P, Cancelli I, Scalise A, Gigli GL. Association of restless legs syndrome in type 2 diabetes: a case-control study. Sleep 2007;30:866–71.
[19] Gemignani F, Brindani F, Vitetta F, Murbini A, Calzetti S. Restless legs syndrome in diabetic neuropathy: a frequent manifestation of small fibre neuropathy. J Peripher Nerv Syst 2007;12:50–3.
[20] Russel JW, Feldman EL. Impaired glucose tolerance. Does it cause neuropathy? Muscle Nerve 2001;24:1109–12.
[21] Ørstavik K, Namer B, Schmidt R, Schmeltz M, Hiliges M, Weidner C, Carr RW, Handwerker H, Jorum E, Torebjork HE. Abnormal function of C-fibres in patients with neuropathy. J Neurosci 2006;26:11287–94.
[22] Gallello M, Setien R, Izquierdo MJ, Casis O, Casis E. Diabetes-induced biochemical changes in central and peripheral catecholaminergic systems. Psysiol Res 2003;52:735–41.
[23] Ondo WG, Zhang X, Xie WJ, Pan TH, Le WD. Clinical correlates of 6-hydroxydopamine injections into all dopaminergic neurons in rats: a possible model for RLS. Mov Disord 2000;15:154–8.
[24] Qu S, Ondo WG, Zhang X, Xie WJ, Pan TH, Le WD. Projections of diencephalic dopamine neurones into the spinal cord in mice. Exp Brain Res 2006;168:152–6.
[25] Handwerker HO, Iggo A, Zimmermann M. segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. Pain 1975;1:147–65.
[26] De Vigili G, Tugnoli V, Penza P, Camozzi F, Lombardi R, Melli G, Broglio L, Granirei E, Lauria G. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain 2008;13(7):1912–25.
[27] Diabetes control and complications research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
[28] Singleton J, Howard J, Goldstein J, Russell J, Feldman E, Peltier A. Diet and exercise compliance decreases neuropathic pain in patients with polyneuropathy associated with prediabetes. Neurology 2005;54:S73.