

Clinical correlates of the restless legs syndrome

Correlações clínicas da síndrome das pernas inquietas

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ABSTRACT

Objective: To determine the clinical correlates of the restless legs syndrome (RLS) in a Brazilian sleep disorders center. **Methods:** We retrospectively studied 118 patients with RLS from January, 2004, to December, 2010. The analyzed variables were: age at disease onset, gender, race, years of school instruction, primary and secondary RLS, and treatment options. **Results:** Among the studied patients, 83.9% were women with a female/male sex ratio of 5:1. Mean age of the patients at symptom onset \pm standard deviation was 41.7 \pm 17.9 years-old. The primary RLS was found in 85% of patients. The other 15% remainders consisted of secondary forms, and they were associated with neuropathy, iron deficiency anemia, end-stage renal disease, or Parkinson's disease. Drug therapy for RLS was introduced in 67% of patients. **Conclusions:** Most patients presented primary RLS with an early disease onset. Further epidemiological studies are welcomed to provide better information on secondary RLS in Brazil.

Key words: restless legs syndrome, restless legs syndrome, epidemiology, Brazil.

RESUMO

Objetivo: Determinar as correlações clínicas da síndrome das pernas inquietas (SPI) em um centro brasileiro de distúrbios de sono. **Métodos:** Foram estudados retrospectivamente 118 pacientes com SPI atendidos entre janeiro de 2004 e dezembro de 2010. As variáveis analisadas compreendiam: idade ao início da doença, sexo, raça, escolaridade, SPI primária e secundária e tratamento da SPI. **Resultados:** Do total de pacientes estudados, 83,9% eram mulheres e a razão mulher/homem foi de 5:1. A média de idade dos pacientes \pm desvio padrão de quando iniciaram sintomas da SPI foi de 41,7 \pm 17,9 anos. Oitenta e cinco por cento dos pacientes apresentaram SPI primária. Os restantes 15% apresentaram a forma secundária, que estava associada à neuropatia periférica, anemia por deficiência de ferro, insuficiência renal crônica e doença de Parkinson. Foi introduzida medicação para SPI em 67% dos pacientes. **Conclusões:** A maioria dos pacientes apresentou SPI primária com início precoce da doença. Mais estudos epidemiológicos são necessários para prover informações sobre as causas secundárias de SPI no Brasil.

Palavras-Chave: síndrome das pernas inquietas, síndrome das pernas inquietas, epidemiologia, Brasil.

The restless legs syndrome (RLS) is a neurological disorder characterized by an urgency to move the legs usually associated with unpleasant sensations in the lower limbs. The symptoms predominate at rest and at night, and they are relieved by leg movements. It may be primary (idiopathic) or secondary to diverse conditions, such as pregnancy, end-stage renal disease, iron deficiency anemia, peripheral neuropathy, and Parkinson's disease¹.

RLS predominates in women and its prevalence in the general population is estimated to range from 5 to 15%. In Brazil, there are few clinical epidemiological studies of RLS²⁻⁴. In this context, our objective was to determine the clinical correlates of patients with RLS in a Brazilian tertiary sleep disorder center.

METHODS

A retrospective case-record analysis was performed in patients with RLS who visited the outpatient Neuro-Sono Sleep Center at the Universidade Federal de São Paulo, from January, 2004, to December, 2010. The Neuro-Sono sleep clinic attends about six new cases per week, totaling 270 new ones per year.

To be included in this study, patients had to fulfill the diagnostic criteria for RLS established by the International RLS Study Group (IRLSG)². Basically, data collected were age at disease onset and at the time of evaluation, gender, race (white or non-white), years of school instruction, and RLS treatment.

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We have searched for secondary causes of RLS (iron deficiency anemia, neuropathy, pregnancy, end-stage renal disease, and Parkinson's disease). We considered with iron deficiency anemia those individuals who performed complete blood count and who had a hypochromic microcytic anemia with low levels of hemoglobin (Hb<13 g/dL for men; Hb<12 g/dL for women). For the diagnosis of peripheral neuropathy, it was necessary to establish clinically the disease and its confirmation by electrophysiological studies. End-stage renal disease was diagnosed in patients who had creatinine clearance <15 mL/min. or who were performing hemodialysis. Two-tailed χ^2 test was performed to access differences between age of symptoms onset in the primary *versus* secondary RLS Groups. Statistical significance was set at $p<0.005$.

We investigated comorbid clinical conditions, such as arterial hypertension, diabetes mellitus, hypothyroidism, depression, smoking, alcohol consumption, fibromyalgia, and other rheumatic diseases taking into account data on medical files.

The clinical data recording over the seven year-protocol was carried out in a systematic manner, using a standard clinical protocol. Even though different physicians of varying degrees of experience participated on data collection, each case on the first consultation and subsequent follow-up was obligatorily discussed with a sleep-disorder specialist, due to the academic nature of our institution. Incomplete or poorly recorded files were excluded from the statistical analysis.

This study protocol is part of a larger study on RLS, and it was approved by our local Ethical Committee (registration number=085005).

RESULTS

A total of 118 patients (women=83.9%; men=16.1%) fulfilled the RLS diagnostic criteria of the IRLSG. The female to male ratio was 5:1, and the mean age at evaluation was 52.4 ± 16.4 years-old. Most patients were white (88%). The mean school instruction was 9 ± 3.1 years-old. Only one patient had no school instruction. Overall, the mean body mass index (BMI) was 26.5 ± 5.5 kg/m².

The range for age at onset in patients with RLS was considerably wide (3 to 81 years-old) with mean age of 41.7 ± 17.9 years-old. Sixty-four patients (55%) had their age at onset of RLS symptoms before 45 years-old (early-onset disease).

In 85% of the patients, we did not find secondary causes of RLS, while the remaining ones (15%) with RLS were associated with peripheral neuropathy, iron deficiency anemia, end-stage renal disease, or Parkinson's disease (Table 1). With respect to the etiology of neuropathy in the affected individuals, seven had diabetic neuropathy and one was of unknown cause. In the group of primary RLS, the average age at onset of RLS symptoms was 41.1 ± 17.6 years-old, while in the group

of secondary RLS, it was 45 ± 19.3 years-old. We did not find significant differences regarding age of symptom onset in the primary *versus* secondary RLS Groups ($p=0.637$).

Drug therapy for RLS was introduced in 67% of our patients and included: pramipexole (n=52; 44%), ropinirole (n=3; 2.5%), levodopa (n=5; 4.2%), gabapentin (n=13; 11%), clonazepam (n=6; 5%), diazepam (n=1; 0.8%), oxcarbazepine (n=2; 1.7%), and carbamazepine (n=3; 2.5%). In our sample, most patients were taking only one medication for symptom control, but seven required one of the following associations: pramipexol plus gabapentin, gabapentin plus clonazepam, and pramipexol plus levodopa. Particularly, the latter association was taken by our patients with Parkinson's disease (n=3; Table 1).

The most frequent clinical comorbid conditions in our sample were: arterial hypertension (n=45; 38.1%), depression (n=35; 27.9%), hypothyroidism (n=18; 14.4%), diabetes (n=9; 7.6%), and fibromyalgia (n=6; 5%). Smoking was found in 5.9% of the patients (Table 2).

Of all patients suspected of RLS, 26 were not included in this study because they did not fulfill the diagnostic criteria established by the IRLSG.

DISCUSSION

In Brazil, there are few studies on epidemiological features of RLS. Dantas et al. studied 32 Brazilian elderly subjects and found a 15% prevalence of RLS, predominantly in females⁵. Moreover, Goffredo Filho et al. evaluated 176 patients on dialysis therapy and found a 14% frequency of RLS⁶. Alves et al., investigating RLS in 524 pregnant women, found a 13.5% prevalence⁷. Recently, Eckeli et al. interviewed 1,155 individuals in the rural town of Cassia dos Coqueiros and estimated a 6.4% RLS prevalence⁴.

Table 1. Secondary causes of the restless legs syndrome.

Causes	Number of patients/ % of patients
Peripheral neuropathy	8/6.8
Iron deficiency anemia	6/5
Parkinson's disease	3/2.5
End-stage renal disease	1/0.8

Table 2. Comorbid conditions in patients with the restless legs syndrome.

Comorbid conditions	Number of patients / % of patients
Arterial hypertension	45/38.1
Depression	35/27.9
Hypothyroidism	18/14.4
Diabetes mellitus	9/7.6
Smoking	8/5.9
Fibromyalgia	6/5

Our study was performed in an outpatient center of sleep disorders, however the methodology used does not allow us to estimate prevalence or incidence rates. Even so, we demonstrated a high predominance of RLS in females and in Caucasians (attributed as white skin color herein), which is consistent with previous epidemiological data of a higher prevalence of RLS in females and Caucasians⁸.

Our data also disclosed a predominance of primary rather than secondary RLS, and our patients with primary RLS had an earlier disease onset (mean age: 41.1±17.6 years-old). Literature in this issue has divided early RLS onset in those patients in whom the first symptoms began before 45 years-old, and possibly they have a genetic and family component⁹. Secondary forms of RLS in our patients were associated with some conditions previously described^{1,2}, and neuropathy was the most frequent condition (44.4%), followed by iron deficiency anemia (33.3%).

Regarding the presence of clinical comorbidities in our patients, we found high frequency of arterial hypertension

and depression. Previous studies have suggested a relationship between RLS and arterial hypertension, but they did not find a clear association of hypertension as a risk factor for RLS¹⁰. On the other hand, epidemiological studies report a two to four risk of depressive disorder in patients with RLS compared with the healthy controls, suggesting an association between both diseases¹¹.

Most patients in our study were taking medication to control the symptoms of RLS, suggesting a higher degree of symptom severity. However, a shortcoming of our study, due to its retrospective methodology, was the lack of graduating patients' RLS severity, alongside with a referral bias that tends to select more severe cases than in the general population.

In summary, our large series of RLS confirms the epidemiological data previously reported elsewhere for non-Brazilian and Brazilian populations and contributes to better understand regional clinical characteristics of our RLS patients.

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