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RESTLESS LEGS SYNDROME IN PATIENTS ON CHRONIC HEMODIALYSIS IN A BRAZILIAN CITY

Frequency, biochemical findings and comorbidities

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ABSTRACT - *Objective*: To evaluate the frequency of restless legs syndrome (RLS) in patients with chronic renal failure (CRF) in Petrópolis, Brazil, and investigate associations between the syndrome and: demographic characteristics, biochemical variables and comorbidities. *Method*: A cross-sectional study in which we interviewed 176 patients on dialytic therapy based on criteria elaborated by the International Restless Legs Syndrome Study Group, and compared data of patients with and without RLS. *Results*: The frequency was 14.8 %. There were no significant differences between the two groups in demographic and biochemical variables investigated (iron, creatinine, intact parathyroid hormone, hemoglobin, calcium, phosphate). We found no association between RLS and the most common comorbidities, except for chronic glomerulonephritis (CGN) (OR = 3.84, $p < 0.01$). *Conclusion*: In the studied population RLS is a common disorder, and is not associated with the investigated biochemical abnormalities. A higher frequency of RLS in subjects with CGN is a finding that needs further investigation.

KEY WORDS: restless legs syndrome, chronic renal failure, chronic glomerulonephritis.

Síndrome das pernas inquietas em pacientes em programa de hemodiálise em Petrópolis, RJ: frequência, aspectos laboratoriais e comorbidades.

RESUMO - *Objetivo*: Determinar a frequência de síndrome das pernas inquietas (SPI) em pacientes com insuficiência renal crônica (IRC) em Petrópolis, Brasil, e investigar associação entre a síndrome e: dados demográficos, achados bioquímicos e comorbidades. *Método*: Estudo transversal no qual entrevistamos 176 pacientes em terapia dialítica a partir de critérios definidos pelo *International Restless Legs Syndrome Study Group*, e comparamos dados de pacientes com e sem SPI. *Resultado*: A frequência foi 14,8 %. Não houve diferença significativa entre os 2 grupos nas variáveis demográficas e bioquímicas (ferro, cretinina, paratormônio, hemoglobina, cálcio, fósforo) investigadas. Não houve associação entre SPI e as principais comorbidades, exceto glomerulonefrite crônica (GNC) (OR = 3,84, $p < 0,01$). *Conclusão*: SPI é condição comum na população estudada, e não é associada com as alterações bioquímicas investigadas. O achado de maior frequência de SPI em pacientes com GNC merece investigações mais detalhadas.

PALAVRAS-CHAVE: síndrome das pernas inquietas, insuficiência renal crônica, glomerulonefrite crônica.

The frequency of restless legs syndrome (RLS) is higher in patients with end-stage renal disease than in the general population, and previous studies have reported it to vary between 17%[1] and 62%[2]. Despite this discrepancy, it is surely an important cause of discomfort and poor quality of life in these subjects. Except for an Asian[2] and a Chilean study[3], there are no data available about prevalence in non-white population[4]. Many other conditions can cause secondary RLS (for example, psychoactive drugs[5]), possibly with different pathophysiological mechanisms. The pathophysiology of RLS in chronic renal failure (CRF) is not established. Investigations have yielded conflicting biochemical data. Anemia[6] and iron deficiency were thought to play a role, but a recent study has failed to demonstrate these correlations[1]. Lower intact parathyroid hormone (iPTH) levels have been found in CRF patients with RLS[1],

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but it is unclear how this biochemical parameter could be related to the syndrome. Peripheral neuropathy is also associated with RLS[7,8]. Although electrophysiologic studies of median, ulnar and sural nerves have not shown a correlation with RLS in CRF patients[9], isolated small sensory fiber loss, undetectable in routine nerve conduction studies, could be an interesting theoretical possibility in this setting, at least for some patients[10]. In RLS patients without CRF, an association between diabetes and RLS is reported[11]. Such a relationship was not found in CRF patients[1], and there are no other data indicating a link between the presence of RLS and comorbidities or the etiology of renal disease in these subjects.

The goals of our study are: to assess the frequency of RLS in CRF patients in a population of different ethnic structure; to reassess metabolic variables in CRF patients with and without RLS, to attempt to establish etiologic or pathophysiologic inferences; to investigate the possible relationship between RLS and comorbidities in CRF patients.

METHOD

Place and patients: We conducted an observational, cross-sectional study in June/2001, in the Hemodialysis Unit in Santa Teresa Hospital, in the city of Petrópolis, Rio de Janeiro State, Brazil. Petrópolis is a city of 300000 inhabitants, 65 kilometers far from Rio de Janeiro, at an altitude of 809 meters. At that time, it was the only hospital in the city that provided a continued dialytic program, and there were 178 patients in the hemodialysis program. Two of them had cognitive deficits, so we interviewed 176 patients.

Interview and definitions: We applied a questionnaire based on the criteria elaborated by the International Restless Legs Syndrome Study Group[12]. The questions were as follows: A) Are there moments in which you have an urge to move your legs, accompanied by sensations of numbness or affliction in the legs? B) Are these sensations worse at rest with at least partial relief by activity? C) Are these sensations worse in any particular period of the day? Which?

The patient was classified as "RLS positive" if answered "yes" for the three questions, and symptoms were worse at evening or night (even if he/she complained of the symptoms also at another period of the day).

We also asked how many times it happened per month or week, and if these symptoms caused insomnia, with prolonged sleep onset latency and/or nocturnal awakening. Additional data were obtained in the interview: age, gender, skin color and smoking.

Biochemical values and associated pathological conditions: Laboratory values (iron, iPTH, hemoglobin, calcium, phosphorus and creatinine) and data about the time he/she had been on a dialysis program, comorbidities and etiology of renal disease were obtained from hospital notes. It is not an easy task to ascribe etiology of chronic renal disease for many patients. Therefore we did not distinguished between comorbidity and etiology for these subjects. All biochemical values were obtained in the month the interviews were done, except for iPTH, which was obtained in the 6-month period before.

Statistical analysis: Continuous variables followed a non-normal distribution, so we used Mann-Whitney test for the analysis, and the chi-square or Fisher exact test, when appropriate, to assess discrete variables. Stratified analysis was performed when necessary, using Mantel-Haenszel weighted (adjusted) odds ratio, to evaluate the presence of confounding.

RESULTS

The group of 176 patients had a mean age of 52 (±13.9) years , and had been on a dialysis program for a mean period of time of 43 (±42) months. There were 107 males (60.8%) and 69 females (39.2%), and 97 subjects were classified as white (55.1%) and 79 as non-white (44.9%).

We found a frequency of RLS of 14.8% (26 subjects; CI 95: 9.9% to 20.9%). Of these, 76.9% patients complained of insomnia (20 subjects; CI 95: 56.4% to 91%). There was only sleep-onset insomnia in 8 patients, only nocturnal awakening in 4 and both in 8 patients. Symptoms of RLS ocurred less than once a week in 5 patients, 1 to 3 times a week in 10 and more than 3 times a week in 11 patients. Three patients reported RLS symptoms only in the dialysis unit, and were not considered as "RLS positive".

We found no significant difference in RLS frequency

Table 1. Biochemical findings in patients with and without RLS.

Variable	Patients With RLS mean (SD)	Patients Without RLS mean (SD)	P-Value
Iron (μmol/L)	1.70(0.27)	1.76 (0.30)	NS
Creatinine (μmol/L)	742.56(265.2)	724.88(265.2)	NS
iPTH (ng/L)	181.9(124.6)	233.2(213.1)	NS
Hemoglobin (μmol/L)	6.57(0.93)	6.64(1.11)	NS
Calcium (μmol/L)	2.19(0.09)	2.22(0.12)	NS
Phosphorus (μmol/L)	1.51(0.12)	1.54 (0.16)	NS

NS, not significant.

Table 2. Frequency of RLS in patients with and without comorbidities.

Comorbidity		Frequency Of RLS%(n)	P-Value
Arterial Hypertension	Present.	14.0%(22/157)	NS
	Absent.	21.0%(4/19)	
Diabetes Mellitus	Present.	17.6%(6/34)	NS
	Absent.	14.0%(20/142)	
Chronic Glomerulonephritis	Present.	32.2%(10/31)	*
	Absent.	11.0%(16/145)	
Tubulointerstitial Disease	Present.	13.3%(2/15)	NS
	Absent.	14.9%(24/161)	

NS, not significant. * $p < 0.01$

comparing non-white and white population (11.4% *v* 17.5%, OR=0.61, CI 95: 0.23 to 1.56) and gender (11.6% in women and 16.8% in men, OR=0.65, CI 95: 0.24 to 1.71). There also was no difference when we compared the mean age of patients with and without RLS (53 *v* 52 years, $p > 0.10$) or the mean time on the dialysis program (31 as 45 months, $p > 0.10$). Smoking habits were not different between subjects with and without RLS ($p > 0.10$).

Biochemical findings are shown in Table 1. There was no significant difference in serum iron, creatinine, iPTH, hemoglobin, calcium or phosphorus between subjects with and without RLS.

The most common pathological conditions associated with CRF were arterial hypertension (89.2 %), diabetes mellitus (19.3%), chronic glomerulonephritis (CGN) (17.6%) and tubulointerstitial disease (8.5%). 3 patients had systemic lupus erythematous, and none of them had RLS. In Table 2, we show the frequency of RLS in patients with and without these comorbidities. We found a statistically significant relationship between CGN and RLS (OR = 3.84, CI 95: 1.40 – 10.51, $p<0.01$). There was no significant relationship between the presence of RLS and arterial hypertension (OR = 0.61, CI 95: 0.17 – 2.41), diabetes mellitus (OR = 1.31, CI 95: 0.42 – 3.87) or tubulointerstitial disease (OR = 0.88, CI 95: 0 – 4.51).

We analyzed separately the subgroup of patients who had CGN, and their demographic and biochemical variables were similar to those found in the entire group, except for skin color (non-whites accounted for 19.4 % and 44.9 %, respectively). The stratified analysis of RLS *as* CGN by skin color disclosed an adjusted OR = 3.37 (CI 95: 1.33 – 8.55), an OR = 2.41 (CI 95: 0.70 – 8.32) in whites and an OR = 11.17 (CI 95: 1.36 – 98.11) in non-whites. When we considered only the subjects with CGN, the frequency of RLS in the entire group was 32.2 % (10/31), in whites was 28 % (7/25) and non-whites was 50 % (3/6).

DISCUSSION

Previous studies yielded very different estimations of RLS prevalence in patients with chronic renal disease, ranging from 17% to 62%. The smaller frequency that we found cannot be ascribed to a single cause. As we used a questionnaire with very strict criteria to consider a patient as "RLS positive", in order to ensure reproducibility, we may have lost sensitivity for the diagnosis. The slight difference we found between white and non-white populations, although not statistically significant, can also have played a role in this question, as the prevalence found in whites was closer to that described by Collado-Seidel et al.[1]. Hui et al.[2] found a much higher prevalence, and it is uncertain if this can be attributed to ethnic variability, difficulty in classifying patients based on clinical subjective criteria, or smaller number of subjects using benzodiazepines. We decided not to investigate the current therapy of our patients, as many of them did not know to inform reliably about their medications.

This study emphasizes RLS as an important cause of sleep disturbance in subjects with CRF, with sleep-onset or sleep-maintenance insomnia. Some patients with RLS did not have insomnia; a reassessment in the future, looking for an aggravation of RLS symptoms, as well as in the patients that did not have RLS, can disclose data that could help us to identify any contributing factor in the pathophysiology of the syndrome. The small difference we found in RLS frequency in ethnic subgroups was not statistically significant. Nevertheless, one cannot assume that this difference does not exist. The ethnic background of the brazilian population is very complex, making it sometimes difficult for us to classify an individual patient, and the generalizability of the results to other populations cannot be ensured, given the unique heterogeneity of the population. Furthermore, larger samples could show significant small differences that we did not find. Last but not least, different prevalences among distinct ethnic groups would be easier to find in patients with primary RLS, in which genetic aspects play a role. In secondary RLS, ethnic factors would certainly be less important than the disease associated with RLS.

Winkelman et al.[9] did not find an association between RLS score and age or sex in patients with CRF, and our study corroborates these findings. Previous

population-based studies found an increasing prevalence of RLS with age[11], and controversial results about gender[11,13]. Unlike primary RLS, it seems that age and gender are not important factors for the development of RLS in CRF subjects. The period of time that the patients had been on dialytic therapy was also unrelated to the presence of RLS, suggesting that the underlying process that originates the syndrome does not depend in a significant manner on any metabolic derangement that occurs after the patient has reached end-stage renal failure.

Data in population-based studies[11,13] about correlation between RLS and smoking was controversial. Many of our patients might have felt ashamed or frightened when asked about smoking habits, so we cannot attest the reliability of our results.

We found no association between any of the biochemical parameters studied and RLS. Unlike the results showed by Collado-Seidel et al.[1], the difference in iPTH levels was small and not significant. Considering this finding and the absence of correlation of calcium and phosphorus concentration and the presence of RLS, as demonstrated by the present and previous studies[1,9], we consider that hyperparathyroidism is not an important factor in the development of the syndrome in CRF patients. It is well known that iron deficiency can play a role in the pathophysiology of the syndrome in patients without renal disease[14,15]. Our study, however, corroborates previous findings indicating that in CRF it is not significantly implicated in the mechanism of the disease[1,9]. From another point of view, recent data demonstrated that even when serum ferritin levels are not reduced, an alteration in iron tranport across blood-brain barrier can account for low brain iron concentrations associated with RLS[16]. Iron uptake in central nervous system is a complex mechanism, in which many intracellular endothelial processes are necessary[17]. We hypothesize that uremia, with its wide consequences in cellular physiology, can interfere with iron uptake across blood-brain barrier and originate iron deficiency in cerebral tissue, similar to that found in some patients with idiopathic RLS. This model could explain the development of RLS symptoms in patients with CRF without detectable peculiarities in the biochemical parameters usually investigated.

The absence of a relationship between hypertension or tubulointerstitial nephritis and RLS is not surprising, as these conditions have not been thought to be related to the syndrome. As we found no correlation between diabetes and RLS, we do not consider peripheral neuropathy plays a major role in the pathophysiology of RLS in CRF patients. We did not do electrophysiologic studies in our patients, but at least a small correlation might be present if polineuropathy, caused or aggravated by diabetes, was an important co-factor in the mechanism of the disease. Although there is good evidence of association between RLS and peripheral neuropathy, either large or small fiber disease, this so-called "neuropathic RLS" seems to have pathogenic mechanisms different from what occurs in CRF-associated RLS, in spite of the similarity of clinical manifestations.

The finding of a statistically significant relationship between RLS and glomerulonephritis deserves careful consideration. Renal biopsy was done in all these patients to establish the diagnosis, but the histopathological analysis was not performed in the same laboratory for all of them. Furthermore, many of the biopsy results were not available, and the reported diagnosis were obtained from hospital notes.

We could not find a reasonable pathophysiologic explanation for the correlation we found between RLS and CGN. The immunologic background of glomerulonephritis' pathogenesis, which is a marker of this condition, hardly helps us in this task, for two reasons: first, there is no known contribution of autoimmune mechanisms in the pathogenesis of RLS; second, it would be expected an even larger prevalence of RLS in subjects with systemic lupus erythematous and advanced renal disease, and this also has not been described in the literature up till now. In our study, the 3 subjects with lupus did not have RLS. A larger sample is needed to better investigate this issue. The similarities of almost all demographical and biochemical variables between the entire group and patients with CGN does not yield useful information, and the very small difference we found between crude and adjusted OR for skin color indicates that this variable is not an important confounder in this setting. Actually, the much larger OR in non-white population with CGN suggests the presence of an interaction between CGN and this ethnic characteristic in the genesis of RLS. This issue deserves more specific investigation, as the small number of patients in this subgroup (non-white with CGN) compromises the accuracy of the finding.

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