Restless legs syndrome in patients on maintenance hemodialysis and peritoneal dialysis

Afsoon Emami Naini[1], Maryam Masoumi[2], Mojgan Mortazavi[3], Ali Gholamrezaei[4], Babak Amra[5]

[1] Associate Professor, Department of Nephrology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. [2] Resident, Department of Internal Medicine, School of Medicine And Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran. [3] Assistant Professor, Department of Nephrology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. [4] Research Assistant, Poursina Hakim Research Institute, Isfahan, Iran. [5] Professor, Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

BACKGROUND: Restless legs syndrome (RLS) is highly frequent among uremic patients; however, little is known about RLS risk factors in these patients. We evaluated the frequency of RLS and associated risk factors in Iranian patients on maintenance hemodialysis (HD) and peritoneal dialysis (PD). **METHODS:** Ninety patients on maintenance HD (n=45) and PD (n=45) were included from two medical centers. Diagnosis of RLS was based on the International Restless Legs Syndrome Study Group criteria, confirmed by the validated Cambridge-Hopkins questionnaire. Patients were tested for iron state, folate, vitamin B_{12}, kidney function and electrolytes. **RESULTS:** Patients included 53 males and 37 females with the mean age of 54.2 ± 15.2 years and disease duration of 5.3 ± 4.5 years. RLS was diagnosed in 26.6% of the patients (35.1% in females vs. 20.7% in males, p = 0.019). RLS was more frequent in HD than PD patients (35.5% vs. 17.7%, p = 0.048), and in those with positive family history of RLS (37.5% vs. 4.5%, p < 0.001). Based on multivariate analysis, female gender [odds ratio (OR) = 6.67], being on HD (OR = 15.9), positive family history (OR = 19.1), higher body mass index (OR = 1.19), and higher serum transferrin (OR = 1.04) and lower total iron-binding capacity (OR = 0.96) levels were associated with risk of RLS. **CONCLUSIONS:** RLS was frequent in patients on maintenance dialysis and female gender, family history of RLS, being on HD, body mass index and iron deficiency were associated with the risk of RLS. Further studies are required for better understanding of RLS pathophysiology and possible treatments in uremic patients.

KEYWORDS: Restless Legs Syndrome, End-stage Renal Disease, Hemodialysis, Peritoneal Dialysis, Risk Factors

BACKGROUND

Different types of sleep complaints have been reported for up to 80% of patients with chronic renal failure (CRF). Several studies showed that sleep apnea, restless legs syndrome (RLS), periodic limb movement disorder (PLMD), and daytime sleepiness are common sleep problems in these patients.[1] RLS in particular has been associated with increased risk of mortality for patients with CRF. [2,3] RLS is a neurological movement disorder that is often associated with sleep disturbances. Patients with RLS have irresistible desire to move their legs during the rest often described as an unpleasant feeling in the legs. [2,4] Estimates of the prevalence of RLS are between 4% and 29% in Western populations, [5] 8% in Iranian population, [6] and between 6.6% to 83% in patients on maintenance dialysis. [7]

The etiology and pathophysiology of RLS is not fully known. Currently, genetic predisposition, dopaminergic dysfunction, and defects in iron metabolism are known as major causes of RLS. Among the causes of secondary RLS are iron deficiency, low serum ferritin levels, folate deficiency, neuropathy, CRF, and diabetes. [4] Dopaminergic system plays a main role in RLS as autopsy reports indicate tyrsoine hydroxylase is increased in substantia nigra for RLS and striatal D2 receptors are decreased in patients with more sever RLS. [8,9] A replicated positron emission tomography (PET) study has shown decreased membrane bound striatal dopamine transporter (DAT) with RLS. [9] RLS symptoms improve with low-dose levodopa, and using dopamine antagonists such as metoclopramide can exacerbate the symptoms. [10]

Iron deficiency is also associated with RLS and iron administration can improved the symptoms.[4] Animal studies show that decreased brain iron produces the RLS dopaminergic profile of increased dopamine activation matched by down regulation of the receptors. [8] Studies have shown that iron and ferritin concentrations are lower and transferrin is higher in CSF of the patients with RLS. [11,12] It is assumed that RLS in CRF and also in pregnancy may be partially related to iron deficiency, [4] and some evidence demonstrated beneficial effects of iron therapy on RLS in these patients. [13,14]

RLS in uremic patients significantly affects their quality of life.[15] Furthermore, according to several reports, there is a significantly higher risk of mortality in CRF patients with RLS. [2,3,16] Thus, accurate and early diagnosis of RLS can lead to a significant improvement in quality of life, and probably overall mortality. [15] Few studies, however, has been conducted on sleep disorders in patients undergoing dialysis in our society. In addition, there are limited data on the risk factors of RLS in uremic patients, especially with regard to the type of dialysis, peritoneal dialysis (PD) versus hemodialysis (HD). Accordingly, we aimed to evaluate the frequency of RLS and associated risk factors in Iranian patients on maintenance HD or PD.

METHODS

Patients and settings

This cross-sectional study was conducted between Jan and Dec 2011 on patients with end-stage renal disease (ESRD) who were on maintenance HD or PD in two academic medical centers in Isfahan (IRAN). Inclusion criteria were at least 18 years of age and a current history of at least 12 weeks of dialysis. Patients with a history of prior hospitalization within 4 weeks before the study were not enrolled. Consecutive consenting case sampling was conducted and with regard to the overall prevalence of RLS = 30%, sample size was calculated as 80 cases. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences and an informed consent was obtained from all patients.

Assessments

During an interview with a trained resident of internal medicine, a questionnaire regarding disease and dialysis characteristics and RLS symptoms was completed.

Diagnosis of RLS and its severity

Patients were screened by a questionnaire for the 4 essential diagnostic criteria for RLS as defined by the International Restless Legs Syndrome Study Group (IRLSSG):[17] "(1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs, which (2) begin or worsen during periods of rest or inactivity, and (3) are partially or totally relieved by movement, and (4) are worse in the evening or night than during the day or only occur in the evening or night." Patients whose responses indicated a diagnosis of RLS were requested to further answer the IRLSSG Severity Scale (IRLS) and Cambridge-Hopkins RLS questionnaire (CH-RLSq). The IRLSSG severity scale includes 10 questions about the severity and frequency of RLS symptoms. Each item is scored from 0 to 4. Based on total score, the severity is categorized to mild (score 1-10), moderate (score 11-20), severe (score 21-30), and very severe (score 31-40) case of RLS.[18] The CH-RLSq is a self-administered questionnaire with a high sensitivity and specificity for the diagnosis of RLS.[19] The questionnaire includes 22 items with 7 of the items for diagnosis and the remaining for better description of the symptoms. Based on responses the patient is classified to definite or probable cases of RLS or no RLS. The most important characteristic of this instrument is its ability to distinguish RLS from those characteristics that can mimic symptoms of RLS (e.g. leg cramps). For using the instrument in our population, the CH-RLSq was linguistically validated with the standard forward-backward translation method.[20]

Laboratory assessments

Patients were tested for complete blood counts, serum iron, ferritin, total iron binding capacity (TIBC), folate, vitamin B_{12}, transferrin, albumin, calcium, phosphorus, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), and fasting blood sugar (FBS). Blood samples were taken in the morning in almost all patients in one clinical laboratory center.

Data Analyses

Data were analyzed using the SPSS software for windows (version 16.0) (SPSS Inc., Chcago, IL, USA). Patients were categorized to those with and without RLS. Comparisons between categorical variables were performed using the Fisher's exact or chi-square test. Student's t-test and Mann–Whitney test were used for comparison of parametric and non-parametric data, respectively. Multivariate regression analysis was also performed to find factors associated with RLS. Statistical significance was defined at the 95% level ($p < 0.05$). Because not all comparisons had a predefined 1-tailed hypothesis we reported 2-tailed p values for all comparisons.

RESULTS

During the study period, 45 patients on HD and 45 patients on PD were evaluated. They consisted of 53 males and 37 females with the mean age of 54.2 ± 15.2 years and disease duration of 5.36 ± 4.56 years. Erythropoietin was prescribed in 60 patients (66.7%; weekly dose: 4877 ± 4595 U. Oral and intravenous iron supplements were prescribed in 29 patients (32.2%), and vitamin B_{12} was prescribed in 58 patients (64.4%). None of the patients were treated with a dopamine agonist. Demographic data and disease characteristics are presented in table 1. Based on the IRLSSG diagnostic crite-

ria, 28.8% of the patients were diagnosed with RLS. The RLS diagnosis was not confirmed by the CH-RLSq for two of these patients, leaving 24 (26.6%) with confirmed RLS. Two (8.3%) of the patients with RLS reported symptoms prior to dialysis and four patients (16.7%) reported that RLS symptoms become worse during dialysis.

Table 2 represents clinical characteristics of patients on HD compared with those on PD. Compared with patients on PD, those who were on HD had longer disease duration (p < 0.001), lower body mass index (BMI, p = 0.013), less hypertension (p = 0.037), lower calcium (p = 0.003) and higher phosphate (p < 0.001), lower BUN (p = 0.044) and creatinine (p < 0.001), and higher albumin (p < 0.001) and ferritin levels (p = 0.001).

Table 1. Clinical and demographic characteristics of patients	
Age (year)	54.2 ± 15.2
Gender (Female/Male)	37 (41.1%)/53 (58.8%)
BMI (kg/m^2)	23.9 ± 4.4
ESRD duration (year)	5.36 ± 4.56
ESRD etiology	
Diabetes	36 (40%)
Hypertension	24 (26.6%)
Glomerulonephritis	7 (7.7%)
Other	14 (15.5%)
Unknown	9 (10%)
Comorbid diseases	
Hypertension	70 (77.7%)
Diabetes	40 (44.4%)
Ischemic heart disease	28 (31.1%)
RLS based on IRLSSG Criteria	26 (28.8%)
RLS Based on CH-RLSq	24 (26.6%)
RLS severity on IRLSSG Rating Scale	
Mild (1-10)	7 (29.1%)
Moderate (11-20)	15 (62.5%)
Severe (21-30)	2 (8.3%)

Data are shown as mean±SD or number (%)
BMI: Body mass index, ESRD: End-stage renal disease, RLS: Restless legs syndrome, IRLSSG: International restless legs syndrome study group, CH-RLSq: Cambridge-Hopkins restless legs syndrome questionnaire

Table 2. Clinical and demographic characteristics of patients on hemodialysis and peritoneal dialysis			
	Hemodialysis N = 45	Peritoneal dialysis N = 45	P-value
Age (year)	54.5 ± 15.0	54.0 ± 15.6	0.875*
Gender (Male/Female)	25(55.5%)/20(44.4%)	28(62.2%)/17(37.7%)	0.334**
ESRD duration (year)	7.4 ± 5.3	3.3 ± 2.2	< 0.001*
BMI (kg/m^2)	22.7 ± 3.9	25.0 ± 4.5	0.013*
Family history	7 (15.5%)	5 (11.1%)	0.379**
Diabetes	20 (44.4%)	20 (44.4%)	0.584**
Hypertension	31 (68.8%)	39 (86.6%)	0.037**
Hemoglobin (g/dL)	11.4 ± 1.8	12.0 ± 1.6	0.130*
CRP (mg/L)	6.6 ± 10.9	6.9 ± 11.6	0.892***
Calcium (mg/dL)	8.16 ± 1.04	8.71 ± 0.59	0.003*
Phosphate (mmoL/L)	5.48 ± 1.35	4.04 ± 0.85	< 0.001*
BUN (mg/dL)	54.7 ± 16.8	65.6 ± 31.4	0.044*
Creatinine (mg/dL)	4.32 ± 2.21	7.38 ± 3.22	< 0.001*
Albumin (g/dL)	4.0 ± 0.43	3.43 ± 0.47	< 0.001*
Ferritin (ng/dL)	496.4 ± 317.6	285.6 ± 266.2	0.001***
Iron (µg/dL)	79.7 ± 32.4	81.6 ± 34.2	0.784*
Transferrin (mg/L)	18.6 ± 3.8	19.4 ± 4.2	0.340*
Transferrin saturation (%)	44.4 ± 20.3	43.9 ± 21.5	0.906*
TIBC (µg/dL)	291.2 ± 42.6	282.5 ± 62.7	0.445*
Vitamin B$_{12}$ (pg/mL)	630.4 ± 514.3	559.9 ± 353.6	0.837***
Folate (ng/mL)	144.8 ± 66.9	149.5 ± 73.6	0.596***

Data are shown as mean ± SD or number (%)
BMI: Body mass index, ESRD: End-stage renal disease, CRP: C-reactive protein, BUN: Blood urea nitrogen, TIBC: Total iron binding capacity
* Independent Sample t-test
** Chi-square or Fisher's exact test
*** Mann-Whitney Test

Table 3. Clinical and demographic characteristics of patients with and without RLS

		With restless legs syndrome N = 24	Without restless legs syndrome N = 66	Pp
Age (year)		55.1 ± 12.9	53.9 ± 16.1	0.753*
Gender (Male/Female)		11(45.8%)/13(54.1%)	42(63.6%)/24(36.3%)	0.019**
Dialysis type	HD	16 (66.6%)	29 (43.9%)	0.048**
	PD	8 (33.3%)	37 (56.0%)	
Hemodialysis dose (h/wk)		10.8 ± 1.8	10.7 ± 1.8	0.956*
Peritoneal dialysis frequency (per day)		4.0 ± 0.5	4.0 ± 0.9	0.937*
ESRD duration (year)		6.5 ± 5.0	4.9 ± 4.3	0.130*
BMI (kg/m^2)		25.1 ± 5.7	23.4 ± 3.7	0.100*
Family history		9 (37.5%)	3 (4.5%)	< 0.001**
Diabetes		10 (41.6%)	30 (45.4%)	0.470**
Hypertension		20 (83.3%)	50 (75.7%)	0.324**
Hemoglobin (g/dL)		11.8 ± 1.5	11.6 ± 1.8	0.568*
CRP (mg/L)		9.3 ± 16.1	5.8 ± 8.7	0.913**
Calcium (mg/dL)		8.31 ± 0.82	8.48 ± 0.91	0.419*
Phosphate (mmoL/L)		5.1 ± 1.5	4.6 ± 1.2	0.064*
BUN (mg/dL)		64.7 ± 23.3	58.6 ± 26.5	0.333*
Creatinine (mg/dL)		5.99 ± 2.82	5.80 ± 3.28	0.806*
Albumin (g/dL)		3.92 ± 0.52	3.68 ± 0.54	0.069*
Ferritin (ng/dL)		328.5 ± 274.5	413.7 ± 320.9	0.454**
Iron (µg/dL)		77.8 ± 28.3	81.7 ± 34.9	0.621*
Transferrin (mg/L)		20.3 ± 3.8	18.6 ± 4.0	0.072*
Transferrin saturation (%)		38.7 ± 12.8	46.2 ± 22.8	0.054*
TIBC (µg/dL)		298.7 ± 49.8	282.5 ± 54.4	0.281*
Vitamin B$_{12}$ (pg/mL)		625.4 ± 499.4	584.1 ± 420.3	0.906**
Folate (ng/mL)		138.3 ± 66.7	150.3 ± 71.3	0.308**

Data are shown as mean ± SD or number (%)
BMI: Body mass index, ESRD: End-stage renal disease, CRP: C-reactive protein, BUN: Blood urea nitrogen, TIBC: Total iron binding capacity
* Independent sample t-test
** Chi-square or Fisher's exact test
*** Mann-Whitney test

Table 4. Multivariate logistic regression analysis on possible risk factors for restless legs syndrome

Adjusted variables	B	P-value	OR	95% CI for OR Lower	95% CI for OR Upper
Female	1.898	0.013	6.671	1.486	29.940
Family history	2.952	0.003	19.153	2.655	138.180
Hemodialysis	2.771	0.003	15.973	2.606	97.889
BMI	0.178	0.032	1.195	1.015	1.407
Iron	0.012	0.298	1.012	0.989	1.035
Ferritin	-0.003	0.102	0.997	0.994	1.001
Transferrin	0.042	0.037	1.043	1.003	1.085
TIBC	-0.032	0.031	0.968	0.940	0.997
CRP	0.035	0.262	1.036	0.974	1.101
Folate	-0.057	0.247	0.945	0.858	1.040
Vitamin B$_{12}$	0.000	0.646	1.000	0.999	1.002

BMI: Body mass index, CRP: C-reactive protein, TIBC: Total iron binding capacity

Comparing the clinical characteristics of patients with and without RLS by univariate analysis is presented in table 3. RLS was present in 35.1% (13/37) of females and 20.7% (11/53) of male patients (p = 0.019).

RLS was more frequent in HD (35.5%) than PD (17.7%) patients (p = 0.048). Nine (37.5%) of the patients with RLS had a history of RLS in their first degree relatives compared with three (4.5%) of those without RLS (p < 0.001). The differences between RLS and non-RLS patients regarding phosphate, albumin, transferrin, and transferrin saturation were not statistically significant and no significant difference was found regarding other variables (p > 0.005).

The results of multivariate logistic regression analysis are presented in table 4. Major predictors were female gender (OR = 6.671), being on hemodialysis (OR = 15.973), and positive family history (OR = 19.153). Other factors associated with risk of RLS included higher BMI (OR = 1.195), and higher transferrin (OR = 1.043) and lower TIBC (OR = 0.968) levels.

DISCUSSION

Several reports are available on the prevalence of RLS and different types of sleep disorders among patients on maintenance hemodialysis; however, few studies have compared the prevalence of RLS between patients on PD and HD and evaluated associated risk factors. Similar to other reports, we found a high frequency of RLS in patients on dialysis (26%) which is considerable compared to our general population (11% in 40-79 years old population).[6] By multivariate analysis we found that female gender, positive family history, and being on HD are major predictive factors for the presence of RLS. Higher BMI, higher levels of transferrin, and lower levels of TIBC are also associated with higher risk of RLS in uremic patients on maintenance dialysis. The association of lower levels of ferritin with RLS was not statistically significant which might be related to the small sample size of the study. Other factors including serum iron, folate, and vitamin B_{12} levels were not associated with RLS. Factors such as duration of ESRD, phosphorus, and albumin that were different between those with and without RLS in univariate analyses were not associated with RLS in multivariate analysis.

Previous studies reported different frequencies of RLS and associated factors in patients on HD and PD. RLS among patients on HD was reported from about 20%[16,21-23] to 60%[24] and most studies with large sample sizes reported a frequency from 30% to 50%.[25-29] Only few reports are available on the association of dialysis type with RLS. Hui et al. reported RLS in 62% and 70% of the patients on PD and HD, respectively.[30,31] Another study by Unruh et al. on a large sample of patients on HD and PD showed sever symptoms

of RLS in 15.6% of HD and 13.3% of PD patients.[3] The other study by Al-Jahdali showed higher prevalence of sleep apnea (92% vs. 67%) and RLS (69% vs. 46%) in PD than in HD patients. [32] However, in the mentioned study, PD and HD patients were not similar in some important factors; PD patients were more obese, had higher frequency of hypertension, had lower dialysis adequacy, and fewer EPO and iron supplementation which according to some reports may have effects on the risk for RLS. [21,33]

Differences between studies might be related to several factors including diagnostic approach to RLS, racial differences, and the studied population. [34] In the study by Cirignotta et al., 50% of HD patients had RLS based on the IRLSSG criteria for RLS, but only 33.3% received a clinical diagnosis of RLS by neurologist.[27] This subject was also shown in one study on a large sample which were interviewed by the Hopkins telephone diagnostic interview and showed that a variety of conditions, including cramps, positional discomfort, and local leg pathology can mimic RLS by fulfilling the 4-item diagnostic criteria of IRLSSG. [35] Similarly, we found that the two patients who had RLS based on the 4-item diagnostic criteria were not RLS cases when interviewed by the CH-RLSq. These results shows that a simple screening questionnaire, with four essential diagnostic criteria of RLS, has limited specificity for diagnosis of RLS in uremic patients which seems to be caused by the frequent presence of other leg symptoms such as pain, paresthesias, itching, and cramps and peripheral neuropathy in uremic patients and thus further clinical interview and examination by an expert is necessary to confirm the diagnosis.

Several studies have conducted to find risk factors for RLS in patients with chronic kidney disease. Evaluated factors were included age, gender, duration of ESRD, type of dialysis, dialysis shift and adequacy, underlying cause of ESRD/concurrent diseases, and biochemical findings mostly including serum iron, ferritin, transferrin, folate, vitamin B_{12} and electrolytes. Female gender has been found to be associated with RLS not only in ESRD patients[26,36] but also in general population. [37] The results of the association between age and RLS in ESRD patients have been controversial, [23,38,39] while studies with larger sample size showed that age is independently associated with severe symptoms of RLS, [3] and that the prevalence of RLS increased with age in the general population. [37,40] Siddiqui et al. showed that duration of being on dialysis is associated with increasing risk of RLS (RR 1.06 per year);[36] however, in other studies duration of uremia was not associated with RLS,[22,38,39] which shows that

RLS in ESRD patients is a multifactorial complaint and not simply affected by the disease duration. Dialysis type as a risk factor for RLS, independent of other factors, has been evaluated only by few studies. As mentioned above, the higher frequency of RLS in patients on PD vs. HD in the Al-Jahdali study was probably affected by differences between patients on dialysis types regarding covariate factors. Nonetheless, our multivariate analysis showed that HD versus PD is a major independent risk factor for RLS. This association cannot be justified by differences between HD and PD patients in the evaluated clinical characteristics as patients on HD had lower BMI, less hypertension, and higher ferritin levels, which are supposed to be associated with lower risk of RLS. HD patients had longer disease duration and lower calcium and higher phosphate levels, but considering these factors in multivariate analysis did not change the outcome. Therefore, other factors related to HD compared with PD must be considered as possible mechanisms by which HD patients are at a greater risk for RLS compared with PD patients.

Dialysis adequacy is a factor that was not associated with RLS in some studies[39, 41] but we found no association between dialysis dose (HD hours per week or PD frequency per day) and RLS. In contrast, a large cohort study on Taiwanese HD patients showed that lower dialysis dose increased the likelihood of daytime sleepiness, RLS and sleep apnea.[33] Regarding dialysis shift, Hsu et al. found a beneficial effect of evening HD, compared with morning and afternoon HD, on sleep quality and reduction of daytime symptoms,[42] while in another study, dialysis shift was not associated with RLS.[25] Our ample was not large enough for such comparison as we only had one patient not receiving evening HD.

Regarding the underlying cause of ESRD/ concurrent diseases, three studies found[3,43,44] and one study did not found[34] any association between diabetes and symptoms of RLS and one study also reported an association between hypertension and RLS in ESRD patients.[21] There is ample of evidence showing the association of diabetes and hypertension as well as obesity with RLS in general population,[45] which indicates that metabolic syndrome components play a significant role in the development and progression of RLS.[46] In our study, higher BMI was independently associated with higher risk of RLS; however, we did not find an association of diabetes or hypertension with RLS which might be attributed to the fact that in uremic patients several other factors can also contribute to RLS symp-

toms and our sample size was not large enough for a comprehensive multivariate analysis.

Deficiencies in iron metabolism play a major role in the pathogenesis of RLS.[4] However, previous studies reported controversial results in ESRD patients. Some studies showed the association of RLS with low iron levels in uremic[25] as well as transplant patients.[47] But, similar to some other reports,[22,29,32] we found no association between serum iron level and risk of RLS. In our study; however, higher levels of transferrin, indicating an iron deficiency state, were associated with higher risk of RLS. We also found lower transferrin saturation in RLS compared with non-RLS cases. Lower transferrin saturation has been shown as an independent risk factor for RLS in CRF patients with heart failure,[48] but another study in these patients[43] and also the study in HD patients did not confirmed this finding.[42] The association of lower levels of ferritin with RLS was not statistically significant in our study which might be related to the small sample size or the inflammatory processes increasing ferritin. Nonetheless, other studies also did not found an association in this regards.[22,36,38,41,42,49] These inconsistent findings reflect both limitations in diagnoses and the problems assessing iron status in these patients, but overall indicate a major role for iron status in RLS with dialysis.

Regarding the effect of iron supplementation on RLS symptoms in ESRD patients, one study showed that high-dose iron infusion results in a transient reduction in the symptoms of RLS in patients with ESRD.[13] Another study; however, on CRF patients with heart failure did not find beneficial effects of EPO and intravenous iron therapy on RLS symptoms.[43] While these findings are not conclusive, they warrant the measurement of serum iron, ferritin, transferrin, transferrin saturation and TIBC in patients with RLS and appropriate therapy when results indicated an iron deficiency state. Iron therapy may also be considered when ferritin levels are within normal range, as patients with functional, but not absolute, iron deficiency may still respond.[13] Similar to other studies, we found no association between folate or vitamin B_{12} and RLS in uremic patients.[29,46]

CONCLUSIONS

The results of the present study showed that RLS is frequent in uremic patients on maintenance dialysis and female gender, positive family history, and being on HD were major risk factors for developing RLS in these patients. We found that higher BMI and iron de-

ficiency were associated with higher risk of RLS in patients on maintenance dialysis. Further studies with larger sample size are required for better understanding of RLS pathophysiology and thus possible treatments in these patients.

ACKNOWLEDGMENTS

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