Neurol Sci (2015) 36:723–727
DOI 10.1007/s10072-014-2026-8

ORIGINAL ARTICLE

Restless legs syndrome in hemodialysis patients in Iran

Mohammad Rohani · Mahbubeh Aghaei · Arya Jenabi · Sharare Yazdanfar · Delaram Mousavi · Shahnaz Miri

Received: 8 September 2014 / Accepted: 28 November 2014 / Published online: 5 December 2014

Abstract Restless legs syndrome (RLS) is a common sleep disorder that can present secondary to medical conditions such as renal failure. This study aimed to evaluate RLS frequency and its related factors in chronic renal failure patients treated with hemodialysis. In a cross-sectional design, 163 patients with chronic renal failure were consecutively enrolled from hemodialysis center at Rasool-Akram hospital. Demographics, clinical and laboratory data were recorded. Patients were screened for presence and severity of RLS according to the four International Restless Legs Syndrome Group (IRLSSG) diagnostic criteria and severity scale. Patients with and without RLS were compared using SPSS statistical software (Version 16.0). Sixty-one patients (37.4 %) were diagnosed with RLS. Mean age in RLS group was significantly higher (65.2 ± 9.3 years) than RLS-negative group (59.0 ± 14.7 years; $P = 0.004$). Serum creatinine level was significantly higher in patients with RLS (7.6 ± 2.1 mg/dl vs. 6.7 ± 1.8 mg/dl; $P = 0.009$). Glomerular filtration rate in RLS patients was lower than other patients (9.2 ± 3.1 ccs/min vs. 11.6 ± 4.8 ccs/min; $P = 0.0001$). Patients with RLS had shorter sleep duration, and higher incidence of insomnia, daytime sleepiness, and sedative-hypnotic medication usage ($P < 0.05$). There was no significant difference between RLS-positive and RLS-negative patients in terms of renal failure pathology, dialysis frequency per week, dose of dialysis, duration of dialysis, renal transplantation, and history of diabetes and hypertension. Hemodialysis patients have a high prevalence of RLS which deserves special attention and specific treatment.

Keywords Restless legs syndrome · Chronic renal failure · Hemodialysis · Sleep disorder

M. Rohani · M. Aghaei · D. Mousavi
Department of Neurology, Iran University of Medical Sciences, Tehran, Iran

A. Jenabi
Department of Nephrology, Iran University of Medical Sciences, Tehran, Iran

S. Yazdanfar
Tehran University of Medical Sciences, Tehran, Iran

S. Miri (✉)
Department of Neurology, SUNY Downstate Medical center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA
e-mail: shahnaz.miri@downstate.edu

Introduction

Restless legs syndrome (RLS) is a common sleep disorder in general population with the prevalence of 5–15 %. The symptoms present with a disturbing sensation associated with an irresistible urge to move the legs, especially at evening or at night, which can improve with leg movements. This syndrome can be idiopathic or secondary to pathologic conditions such as pregnancy, iron deficiency anemia, neurologic diseases, and renal insufficiency [1–4].

In hemodialysis patients, the prevalence of RLS has been reported between 12 and 62 % [3], and the associated factors are introduced as iron deficiency, vitamin deficiencies, and diabetes mellitus [3]. Furthermore, there are significant associations between RLS and frequency of dialysis per month, serum levels of blood urea nitrogen (BUN) and creatinine in patients with chronic renal failure (CRF) [5]. Renal transplantation significantly improves RLS symptoms, which further confirms the role of renal insufficiency [6].

RLS causes sleep deprivation, daytime sleepiness, depression, reduced quality of life and increased morbidity

in patients with renal failure [3]. RLS increases the cardiovascular risk and mortality in chronic hemodialysis patients [7]. Studies have shown that treatment of sleep disorders in CRF patients can improve the quality of life [4]. The present study aimed to evaluate the frequency and associated factors of RLS in CRF patients treated with hemodialysis.

Methods

This cross-sectional study was conducted in hemodialysis center of Rasool-Akram hospital affiliated to Iran University of medical sciences, during May 2012 to September 2012. The study protocol was approved by the institutional medical ethics committee.

One hundred and sixty-three CRF patients treated with hemodialysis, consecutively enrolled in the study. Inclusion criteria for the study included: being able and willing to give informed consent; being diagnosed with CRF and treated with hemodialysis at least for 1 year; having dialysis at least two times a week. Patients underwent neurological examinations by one neurologist to exclude other secondary neurological causes of RLS. Patients with abnormal neurological exam, including sensory or motor impairments were excluded from the study. Presence of severe infection or acute systemic diseases was other exclusionary criteria. A face to face interview was performed and demographics including age, gender, marital status, education, height, weight and BMI, history of smoking, alcohol and opium consumption were recorded. Patients were asked about duration of night sleep and sleep problems including insomnia, daytime sleepiness, sleep latency, and consumption of sedative-hypnotics.

The type of renal failure, frequency of dialysis per week, duration of dialysis, dialysis dose, history of kidney transplant, diabetes mellitus, and hypertension were recorded from medical records and interview. Laboratory evaluations included hemoglobin level, ferritin, fasting blood sugar, BUN, and creatinine.

Patients were assessed for the presence of RLS by the four criteria of international RLS study group (IRLSSG) during the face to face interview. These criteria include: unpleasant sensations in foots or legs which develop or exacerbate during rest; aggravate in the evening or at night; and relieve with movement. Patients who fulfilled all four criteria considered to have RLS and further evaluated by the self-questionnaire of IRLSSG severity scale. Family history of RLS was also evaluated in RLS-positive patients.

The data were expressed as mean ± standard deviation (SD). Chi square test and *t* test were used for qualitative and quantitative data, respectively. All statistical analyses were performed with SPSS version 16 for Windows (SPSS Inc. Chicago, IL, USA).

Result

A total of 163 hemodialysis treated CRF patients with mean age of 61.3 ± 13.3 years (range 18–82 years) (63.2 % male) were studied. One hundred and eight patients (66.3 %) had complaint of insomnia more than 2 nights per week, and 71 patients (43/6 %) were experiencing daytime sleepiness more than 2 days per week. Average sleep duration at night was 6.2 ± 1.4 h (range 3–10 h). Sixty-seven patients (41.4 %) were taking sedative-hypnotic medications.

Based on the four IRLSSG criteria, 61 patients (37.4 %) were diagnosed with RLS. Mean age of RLS patients was significantly higher than patients without RLS (65.2 ± 9.3 years vs. 59.0 ± 14.7; $P = 0.004$). There was no significant association between RLS and gender, marital status, education, drug usage, drug abuse, alcohol intake, smoking, and BMI. Unemployment was related to presence of RLS ($P = 0.03$) (Table 1).

There was no significant difference between RLS-positive and RLS-negative patients in terms of dialysis frequency and duration, history of renal transplantation, diabetes mellitus and hypertension ($P > 0.05$). However, the prevalence of cardiovascular diseases was significantly higher in RLS-positive patients (32.8 vs. 16.7 %; $P = 0.01$) (Table 2).

No difference was observed between the two groups regarding the hemoglobin level, serum level of ferritin, fasting blood glucose and BUN. However, serum creatinine level in patients with RLS was significantly higher than other patients (7.6 ± 2.1 vs. 6.7 ± 1.8 mg/dl) ($P = 0.009$). Furthermore, glomerular filtration rate (GFR) in RLS-positive patients was significantly lower (9.2 ± 3.1 vs. 11.6 ± 4.8 ccs/min; $P = 0.0001$) (Table 2).

Sleep complaints were more common in RLS-positive patients ($P = 0.0001$). These complaints included shorter duration of sleep, more sleep latency, frequent experience of insomnia and daytime sleepiness, and more common sedative-hypnotic consumption ($P = 0.0001$) (Table 3).

The average RLS severity score was 22.7 ± 7.2 (Max: 40). Three patients (4.9 %) had mild symptoms (score 0–10), 23 patients (37.7 %) had moderate symptoms (score of 11–20), 22 patients (36.1 %) reported severe symptoms (score of 21–30), and 13 patients (21.3 %) had very severe symptoms (score of 31–40). There was no significant association between severity score and age, gender, BMI, serum levels of glucose, blood urea nitrogen, creatinine, ferritin, and GFR ($P > 0.05$). There was an inverse correlation between severity score and hemoglobin levels

Table 1 Demographic features of CRF-Hemodialysis patients with and without RLS

Variable	All patients ($n = 163$)	RLS+	RLS−	P value
Gender				
Female	60 (36.8 %)	24 (39.3 %)	36 (35.3 %)	0.60
Male	103 (63.2 %)	37 (60.7 %)	66 (64.7 %)	
Age (year)	61.3 ± 13.3	65.2 ± 9.3	59.0 ± 14.7	0.004
Marital Status				
Single	27 (16.6 %)	9 (14.8 %)	18 (17.6 %)	0.83
Married	113 (69.3 %)	44 (72.1 %)	69 (67.6 %)	
Widowhood	23 (14.1 %)	8 (13.1 %)	15 (14.7 %)	
Education				
Diploma and lower	102 (62.6 %)	44 (72.1 %)	58 (56.9 %)	0.05
University education	61 (37.4 %)	17 (27.9 %)	44 (43.1 %)	
Employment	57 (35 %)	15 (24.6 %)	42 (41.2 %)	0.03
Drug consumption	25 (15.3 %)	12 (19.7 %)	13 (12.7 %)	0.23
Alcohol intake	19 (11.7 %)	7 (11.5 %)	12 (11.8 %)	0.95
Smoking	77 (47.2 %)	29 (47.5 %)	48 (47.1 %)	0.95
Height (cm)	168.5 ± 8.6	166.5 ± 7.8	169.7 ± 8.9	0.02
Weight (Kg)	67.4 ± 8.6	66.5 ± 7.9	67.9 ± 9.0	0.31
BMI (Kg m^2)	23.6 ± 1.5	23.9 ± 1.8	23.4 ± 1.3	0.07

($P = 0.009$, $r = -0.33$). Positive family history of RLS was reported in 6 patients (9.8 %) and it was not related to age, gender, RLS duration and severity, or laboratory findings ($P > 0.05$).

Discussion

Prevalence of restless legs syndrome in patients with CRF (19–56.4 %) [8–16], especially those treated with hemodialysis (12 and 62 %) [3], has been reported significantly higher than general population (5–15 %) [1–4]. The prevalence of RLS in our hemodialysis patients was 37.4 %. We observed no association between RLS and gender, marital status, education, drug usage, alcohol intake and smoking in hemodialysis treated patients. Salman and colleagues have also reported no association between RLS incidence and sex, nicotine and caffeine consumption [10]. Demographics, smoking, caffeine intake, and higher BMI are recognized as risk factors for RLS in healthy population [1, 2]. Our findings, consistent with previous reports, suggest that demographics features have a lower impact on these patients' population. We only observed the relationship between RLS and higher age in our CRF patients. Pizza et al. (2012) [17] reported a higher rate of positive family history of RLS (22 %) in hemodialysis patients with RLS compared to those without RLS (6 %). Among our RLS-positive patients, 9.8 % had a positive family history of RLS.

Peripheral neuropathy and first-degree relative with RLS are predictive factors of RLS in hemodialysis patients [17, 18]. Peripheral neuropathy in CRF patients can cause moderate severity of leg discomfort which may be misdiagnosed with RLS. Careful neurological exam along with IRLSSG criteria is suggested for RLS evaluation in CRF patients [18].

This study found no association between incidence of RLS and type of renal failure, dialysis frequency, dose and duration of dialysis, history of renal transplant, diabetes and hypertension. Similarly, Nikic and colleagues reported no differences between duration of dialysis and features of hemodialysis in patients with and without RLS [8]. Current study indicates that previous history of ischemic heart disease is associated with RLS. Zilberman and colleagues have shown the high prevalence of RLS in the anemic patients who had chronic renal failure or congestive heart disease (39.4 %) [19]. The finding can be due to negative impact of cardiac failure on renal function which may augment the underlying cause of RLS in CRF patients.

Previous studies have concluded that lower GFR (15–29 ml/min) is a risk factor for RLS [20]. Pizza et al. introduced low or absent residual diuresis as predictive factors of RLS in hemodialysis patients [17]. We observed the association RLS with higher serum creatinine level and lower GFR. Similarly, the study of Nikic and colleagues reported that creatinine level in patients with RLS was higher than other patients, which could be indicative of inadequate dialysis in these patients [8]. Study of Ibrahim and his colleagues showed that sleep disorders and the incidence of RLS are significantly related to inadequate dialysis, hyperphosphatemia, and hypoalbuminemia [9].

The high prevalence of RLS in end stage renal disease patients undergoing hemodialysis can be extremely troublesome. Sleep disorders in hemodialysis patients have been reported from 46 to 61 % [9, 13, 14]. The study by Merlin and colleagues has shown that approximately 80 % of hemodialysis patients have at least one sleep disorder [16]. Prevalence of insomnia and other sleep disturbances in current study was significantly higher than previous studies and these disturbances were more common in RLS-positive patients (88 %). Shorter sleep duration, insomnia, sedative drugs usage, and daytime sleepiness were more common in patients with RLS. Tuncel's study discussed about the quality of Epworth sleepiness scale (ESS) showing that 47 % of hemodialysis patients, especially those with RLS, have sleep disorders [14]. Araujo and colleagues concluded that lower hemoglobin levels in hemodialysis patients are associated with more severe RLS,

Table 2 Characteristics of renal failure, dialysis and laboratory tests in CRF patients with and without RLS

Variable	All patients ($n = 163$)	RLS+	RLS−	P value
Type of renal failure				
Glomerulonephritis	15 (9.2 %)	3 (4.9 %)	12 (11.8 %)	0.13
Vascular nephropathy	36 (22.1 %)	18 (29.5 %)	18 (17.6 %)	
Diabetic nephropathy	84 (51.5 %)	32 (52.5 %)	52 (51.0 %)	
Interstitial nephropathy	24 (14.7 %)	8 (13.1 %)	16 (15.7 %)	
Autoimmune nephropathy	4 (2.5 %)	0	4 (2.5 %)	
Dialysis frequency per week				
2 times	6 (3.7 %)	3 (4.9 %)	3 (2.9 %)	0.51
3 times	157 (96.3 %)	58 (95.1 %)	99 (97.1 %)	
Dialysis dose (Kt.V)	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	0.68
Dialysis duration (year)	1.9 ± 1.4	2.1 ± 1.3	1.8 ± 1.5	0.28
Renal transplantation	9 (5.5 %)	2 (3.3 %)	7 (6.9 %)	0.33
Diabetes	85 (52.1 %)	34 (55.7 %)	51 (50 %)	0.47
Hypertension	80 (49.1 %)	34 (55.7 %)	46 (45.1 %)	0.18
Cardiac diseases	37 (22.7 %)	20 (32.8 %)	17 (16.7 %)	0.01
Hb (mg.dl)	13.0 ± 2.1	12.7 ± 2.0	13.2 ± 2.1	0.20
Serum ferritin (ng.ml)	1238 ± 428	1281 ± 556	1203 ± 287	0.44
FBS (mg.dl)	112 ± 24	113 ± 24	112 ± 24	0.65
BUN (mg.dl)	46.0 ± 12.8	47.2 ± 12.4	45.2 ± 13.0	0.33
Cr (mg.dl)	7.0 ± 1.9	7.6 ± 2.1	6.7 ± 1.8	0.009
GFR (ccs.min)	10.7 ± 4.4	9.2 ± 3.1	11.6 ± 4.8	0.0001

Table 3 Sleep complaints in RLS-positive and RLS-negative patients

Variable	All patients ($n = 163$)	RLS+	RLS−	P value
Duration of night sleep (h)	6.2 ± 1.4	5.4 ± 1.6	6.7 ± 1.1	0.0001
Difficulty in falling sleep	94 (57.7 %)	50 (81.9 %)	44 (43.1 %)	0.0001
Delay in falling sleep (min)	40.6 ± 35.8	62.2 ± 44.0	27.6 ± 21.5	0.0001
Taking sleep medications	67 (41.4 %)	42 (68.8 %)	26 (25.4 %)	0.0001
Insomnia	108 (66.3 %)	54 (88.5)	54 (52.9 %)	0.0001
Daytime sleepiness	71 (43.6 %)	46 (75.4 %)	25 (24.5 %)	0.0001

worse sleep quality, higher scores on the Beck Depression Inventory, more daytime sleepiness and obstructive sleep apnea [15]. Previous studies have shown that undiagnosed RLS can significantly reduce quality of life in CRF patients [11, 19]. Therefore, accurate diagnosis and appropriate treatment of RLS can improve quality of life in these patients.

In conclusion, RLS has a high prevalence in CRF patients treated with hemodialysis. Presence of RLS in hemodialysis patients is related to higher levels of serum creatinine and lower GFR which suggests the direct relationship between renal dysfunction and RLS. Furthermore, this study shows poor sleep as a consequent of RLS in hemodialysis patients which indicates the importance of RLS screening and treatment in these patients population.

Conflict of interest Authors declare no conflict of interest.

References

1. Ekbom K, Ulfberg J (2009) Restless legs syndrome. J Intern Med 266(5):419–431
2. Bayard M, Avonda T, Wadzinski J (2008) Restless legs syndrome. Am Fam Physician 78(2):235–240
3. Molnar MZ, Novak M, Ambrus C, Szeifert L, Kovacs A, Pap J et al (2005) Restless legs syndrome in patients after renal transplantation. Am J Kidney Dis 45(2):388–396
4. Mucsi I, Molnar MZ, Ambrus C, Szeifert L, Kovacs AZ, Zoller R et al (2005) Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. Nephrol Dial Transpl 20(3):571–577
5. Chen WC, Lim PS, Wu WC, Chiu HC, Chen CH, Kuo HY et al (2006) Sleep behavior disorders in a large cohort of Chinese (Taiwanese) patients maintained by long-term hemodialysis. Am J Kidney Dis 48(2):277–284
6. Molnar MZ, Novak M, Ambrus C, Szeifert L, Kovacs A, Pap J et al (2005) Restless Legs Syndrome in patients after renal transplantation. Am J Kidney Dis 45(2):388–396
7. La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML et al (2011) Restless legs syndrome enhances cardiovascular

risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. Nephrol Dial Transpl 26(6):1976–1983
8. Nikić PM, Andrić BR, Stojanović-Stanojević M, Dordević V, Petrović D, Stojimirović BB (2007) Restless legs syndrome prevalence in patients on chronic hemodialysis in central Serbia. Vojnosanit Pregl 64(2):129–134
9. Ibrahim JM, Wegdan OM (2011) Epidemiology of sleep disorders in patients with chronic renal disease in Cairo Egypt. J Egypt Public Health Assoc 86(3–4):68–72
10. Salman SM (2011) Restless legs syndrome in patients on hemodialysis. Saudi J Kidney Dis Transpl 22(2):368–372
11. Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S et al (2004) Restless legs syndrome in end-stage renal disease. Sleep Med 5(3):309–315
12. Merlino G, Lorenzut S, Romano G, Sommaro M, Fontana A, Montanaro D et al (2012) Restless legs syndrome in dialysis patients: a comparison between hemodialysis and continuous ambulatory peritoneal dialysis. Neurol Sci 33(6):1311–1318
13. Malaki M, Mortazavi FS, Moazemi S, Shoaran M (2012) Insomnia and limb pain in hemodialysis patients: what is the share of restless leg syndrome? Saudi J Kidney Dis Transpl 23(1):15–20
14. Tuncel D, Orhan FO, Sayarlioglu H, Isık IO, Utku U, Dinc A (2011) Restless legs syndrome in hemodialysis patients: association with depression and quality of life. Sleep Breath 15(3):311–315
15. Araujo SM, de Bruin VM, Nepomuceno LA, Maximo ML, Daher Ede F, Correia Ferrer DP et al (2010) Restless legs syndrome in end-stage renal disease: clinical characteristics and associated comorbidities. Sleep Med 11(8):785–790
16. Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M et al (2006) Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. Nephrol Dial Transpl 21(1):184–190
17. Pizza F, Persici E, La Manna G, Campieri C, Plazzi G, Carretta E et al (2012) Family recurrence and oligo-anuria predict uremic restless legs syndrome. Acta Neurol Scand 125(6):403–409
18. Cirignotta F, Mondini S, Santoro A, Ferrari G, Gerardi R, Buzzi G (2002) Reliability of a questionnaire screening restless legs syndrome in patients on chronic dialysis. Am J Kidney Dis 40(2):302–306
19. Zilberman M, Silverberg DS, Schwartz D, Oksenberg A (2010) Restless legs syndrome (RLS) in anemic patients with congestive heart failure and chronic renal failure: lack of effect of anemia treatment. Int J Cardiol 143(2):205–207
20. Quinn C, Uzbeck M, Saleem I, Cotter P, Ali J, O'Malley G et al (2011) Iron status and chronic kidney disease predict restless legs syndrome in an older hospital population. Sleep Med 12(3):295–301