



ORIGINAL RESEARCH PAPER

Medicine

MAGNITUDE AND DETERMINANTS OF RESTLESS LEGS SYNDROME IN PATIENTS WITH CHRONIC KIDNEY DISEASE ADMITTED IN A RURAL TERTIARY CARE HOSPITAL.

KEY WORDS: Prevalence, Restless legs syndrome, determinants, Chronic Kidney Disease, hemodialysis.

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ABSTRACT

Background: Restless legs syndrome (RLS) is a common and extremely distressing problem experienced by chronic kidney disease (CKD) patients. RLS is also associated with poor sleep, impaired quality of life, increased incidence of cardiovascular events and higher mortality in CKD patients.

Settings and Design: A cross-sectional hospital-based study was performed in CKD patients admitted in the department of Medicine of a rural teaching tertiary care hospital in central India.

Materials and Methods: In all consecutive CKD inpatients, presence of RLS or its severity was assessed by a trained person through a questionnaire [International Restless Legs Syndrome Study Group (IRLSSG) criteria] who is blind of the comorbidities and investigations of the patient. Another study person collected the data including demographics, co-morbid diseases or risk factors, clinical and laboratory parameters.

Results: Of the total 206 CKD patients, 143 (69%) were males and 63 (31%) were females. Forty-eight (23%) of the 206 CKD patients had RLS. Of the 206 CKD patients, 4 (1.9%) had mild RLS, 15 (7.3%) had moderate RLS, 18(8.7%) had severe RLS and 11(5.3%) had very severe RLS. The association of female gender, hemodialysis, severe anemia and serum ferritin level with RLS was found to be statistically significant ($P < 0.05$).

Conclusion: RLS was present in 23% (approximately one quarter) of patients with CKD and was related to female gender, hemodialysis, severe anemia and serum ferritin levels.

Introduction

CKD is becoming a major global public health problem. Worldwide, an estimated 200 million people have CKD.^[1] In India, results from the SEEK (Screening and Early Evaluation of Kidney Disease) study shows that the overall prevalence of CKD is 17.2% with ~6% have CKD stage 3 or worse.^[2]

Restless legs syndrome (RLS) is characterized by an unpleasant sensations or discomfort in the legs, typically occurs in the evening or early part of the night.^[3] Data from various studies across the globe shows the prevalence of RLS in CKD patients to range between 6.6 and 60%, which is substantially higher than the 5% to 15% prevalence rate in the general population.^[4-11] In patients of CKD, presence of RLS is associated with poor sleep, increased odds for insomnia, substantial morbidity and impaired quality of life in patients with CKD.^[5,6,12] Patients with RLS were more often affected by symptoms of anxiety and depression.^[8, 11, 13] Available evidence from a few studies shows that RLS is associated with an increased incidence of cardiovascular events and higher mortality in CKD patients.^[6,14,15]

As there is uncertainty regarding the frequency and determinants of RLS in CKD patients, this study was planned to assess the magnitude of RLS in CKD patients admitted in a rural tertiary care hospital and to analyse the association of demographic variables, co-morbid conditions and laboratory parameters with RLS.

Materials and methods

Setting and study design

A hospital-based cross-sectional study was conducted between December 1, 2013 and October 31, 2015 in the department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram which is a 750- bedded rural teaching tertiary care hospital located in a town in central India. Most patients visiting the hospital come from rural areas. The patients with the diagnosis of CKD are admitted in the Medicine ward or ICU.

Inclusion criteria

All consecutive patients admitted in Medicine ward/ ICU with a diagnosis of chronic kidney disease, as defined by Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines of the National Kidney Foundation (NKF) i.e. kidney damage or a GFR of less than 60ml/min/1.73 m² for 3 months or longer, 18 years of age or older, who agreed to participate in the study were recruited.^[6]

Exclusion criteria

Patients with acute kidney injury, any malignancy, neurological disorders (stroke, Parkinson's disease, dementia, lumbosacral radiculopathy), chronic obstructive airway disease, pregnancy, rheumatoid arthritis, documented history of mental illnesses requiring psychiatric treatment, taking medications for depression or anxiety, history of chronic liver disease or liver enzymes (ALT/AST) more than 3 times the upper limit of normal were excluded from the study. Patients with problems of communication (e.g. due to reduced level of consciousness, severe hearing impairment, aphasia, cognitive dysfunction and uremic encephalopathy) were also excluded.

Data collection

A research assistant collected the data of CKD patients including demographic variables (age, sex etc.), co-morbidities like hypertension (history of hypertension or anti-hypertensive drugs), diabetes mellitus (DM) [history of DM or anti-diabetic drugs], ischemic heart disease (IHD) and hemodialysis (HD) dependency. History of alcohol consumption (more than 5 standard drinks per day) was also taken. Blood pressure (BP) was recorded in all CKD patients at the time of admission in the Medicine ward/ICU. A mean of three BP readings of each patient was recorded. Reports of laboratory investigations like serum creatinine, urea, sodium, potassium, albumin, calcium, phosphate, hemoglobin, mean corpuscular volume, serum ferritin and ultrasonography of abdomen were collected from patient's medical records. Staging of CKD was assessed by calculating estimated glomerular filtration rate (GFR) using Modification of Diet in Renal Diseases (MDRD) equation.^[6] Severe anemia was defined as hemoglobin < 7 g/dl for both genders according to World Health Organization (WHO) criteria.

Presence of RLS or its severity in patients of CKD was assessed by another trained person who was blind of the co-morbidities and investigation reports of the patients, through a face-to-face interview based questionnaire. RLS was diagnosed according to the criteria of the International RLS Study Group (IRLSSG).^[6] This questionnaire-based RLS diagnosis requires answers consistently indicating presence of all four of the essential RLS diagnostic criteria, i.e.: (1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (2) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (3) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues. (4) The urge to move or unpleasant sensations

are worse in the evening or night than during the day or only occur in the evening or night.

An RLS severity rating scale developed and validated by IRLSSG was used to measure the severity of RLS symptoms.^[7] The total score is calculated and the severity is assessed as- Very severe: 31-40 points, Severe: 21-30 points, Moderate: 11-20 points, Mild: 1-10 points, None: 0 point.

Statistical analysis

We used SPSS software (version 16.0) to analyze the characteristics of the study population. The demographic variables, comorbidities, clinical and biochemical parameters of the CKD patients with RLS were compared with those without RLS using the chi-square test, Fisher exact test, students t-test and the Mann-Whitney U test, as appropriate. P value <0.05 was regarded as being statistically significant.

Results

A total of 206 patients with CKD were studied. The mean age was 48.67 ± 13.52 years, ranging from 16 years to 81 years. Of the total 206 CKD patients, 143 (69%) were males and 63 (31%) were females [Table 1].

Forty-eight patients (23%) of the 206 CKD patients had RLS. Of the 206 CKD patients, 4 (1.9%) had mild RLS, 15 (7.3%) had moderate RLS, 18 (8.7%) had severe RLS and 11 (5.3%) had very severe RLS [Table 2].

The association of age of the patient (<30 years, 30-60 years, >60 years) with RLS was not statistically significant ($P > 0.05$) [Table 1]. Female gender was found to be significantly associated with presence of RLS in our CKD patients ($P < 0.05$) [Table 1]. Of the 206 CKD patients, 122 (59%) had hypertension, 37 (18%) had DM and 20 (10%) had IHD. RLS was not significantly associated with any of the co-morbidities, i.e. hypertension, DM or IHD ($P > 0.05$) [Table 3]. One hundred seventeen (57%) of the 206 CKD patients were on maintenance HD. The magnitude of RLS in CKD patients on maintenance HD was 27 % (32 of the 117 CKD patients on maintenance HD had RLS). Hemodialysis dependence was related to presence of RLS in our CKD patients ($P < 0.05$) [Table 4]. The biochemical parameters like serum creatinine, sodium, potassium, albumin, calcium, phosphate and blood urea did not differ significantly between CKD patients with and without RLS [Table 5]. However, severe anemia (Hb < 7 g/dl) and serum ferritin levels were significantly associated with presence of RLS ($P < 0.05$) [Table 5]. Of the 58 CKD patients having severe anemia, 41 (70.7%) CKD patients had RLS.

Of the total 206 CKD patients, 161 (78%) had stage 5 CKD, 29 (14%) had stage 4 CKD, and 16 (8%) had stage 3 CKD. Staging of CKD (severity) was not associated with presence of RLS ($P > 0.05$).

Discussion

In our study, the overall magnitude of RLS in CKD patients was 23% (48 of the 206 CKD patients had RLS). Of the 206 patients, 4 (1.9%) had mild RLS, 15 (7.3%) had moderate RLS, 18 (8.7%) had severe RLS and 11 (5.3%) had very severe RLS. Similarly, in previous studies RLS prevalence rates of 24.2% and 21.5% were reported by Lee et al. and Gigli et al., respectively.^[8, 18] However, the prevalence of RLS in CKD patients reported in the literature varies from 6.6% to 60%.^[8, 19] The wide variation in the prevalence of RLS in CKD patients in different studies can be attributed to differences in diagnostic criteria applied to diagnose RLS and marked heterogeneity of the study population.

In our study, the association of age with RLS in CKD patients was not found to be statistically significant which is consistent with the result of previous studies.^[8, 20, 22] Kawauchi et al. observed that CKD patients on HD were significantly younger in the RLS group.^[7]

Female gender was significantly associated with RLS in our study. A previous study by Chavoshi et al. also showed a significant association of RLS with female gender.^[22] Two other studies done by Araujo et al. and Berger et al. found a strong association of

female gender with RLS.^[23, 24] These studies demonstrated a two fold increased risk of having RLS with female gender. However, Salman found that gender was not related to RLS in CKD patients in his study.^[20]

Comorbidities such as hypertension, diabetes mellitus, ischemic heart disease and alcohol consumption were not found to be significantly associated with presence of RLS in CKD patients in our study. Similarly, no significant correlation was found between any comorbidity and RLS in previous studies by Salman, Collado-Seidel et al. and Gigli et al.^[8, 20, 25] However, Araujo et al. observed that hypertension was associated with moderate or severe RLS in their study.^[23] Chavoshi et al. found significant association of intake of anti-hypertensive medicines with RLS.^[22] Alcohol can trigger or exacerbate RLS is reported in the literature.^[12]

The magnitude of RLS in CKD patients on maintenance HD was 35 % (34 of the 96 CKD patients on maintenance HD had RLS). In previous studies, RLS prevalence rates of 33.3%, 23% and 14% in CKD patients on hemodialysis were reported by Walker et al., Kawauchi et al. and Musci et al., respectively.^[8, 5, 7] Hemodialysis dependence was related to presence of RLS in CKD patients in our study. This result was similar to the results of Gigli et al., but dissimilar to the results of Salman, Riar et al. and Collado-Seidel et al.^[8, 20, 25, 26] The possible explanation for the association of hemodialysis with RLS might be related to increased loss of iron as a result of chronic blood loss in CKD patients on hemodialysis. Also, hemodialysis may restrict movement of limbs during the hemodialysis treatment (for approx. 4 hours) which may precipitate RLS symptoms.

The biochemical parameters like serum creatinine, sodium, potassium, albumin, calcium, phosphate and blood urea did not differ significantly between CKD patients with and without RLS which is in line with the results of Salman and Collado-Seidel et al.^[20, 25] However, symptoms of RLS were related to urea and creatinine levels in the study of Walker et al.^[8] Scores of RLS severity were correlated significantly with serum phosphate, calcium and albumin in a study done by Neves et al.^[27] Kawauchi et al. demonstrated an association of serum calcium levels with RLS in their study.^[7]

In our study, severe anemia and serum ferritin levels were significantly associated with the presence of RLS in CKD patients which is in line with the results of Roger et al., Araujo et al., and O'Keefe et al.^[23, 28, 29] Earley et al. found that patients with RLS had lower CSF ferritin levels.^[30] The improvement in the RLS symptoms on treatment with intravenous iron supplements and erythropoietin as observed in the previous studies support our study findings.^[31] Presence of RLS was not related to the staging of CKD (severity) in our study which is in line with the result of Lee et al.^[8] Riar et al. also reported that severity of CKD was not related to the presence of RLS in pediatric CKD patients.^[26]

The pathophysiology of RLS is not fully understood, and may be multifactorial. Dopaminergic dysfunction and brain iron deficiency have long been regarded as the key culprits in the pathophysiology of RLS.^[8, 12, 32, 33]

Conclusion

Restless legs syndrome was present in 23% (approximately one quarter) of patients with CKD. RLS was significantly associated with female gender, hemodialysis, severe anemia and serum ferritin levels.

Suggestion

This study shows that RLS is common in CKD patients. RLS in CKD patients is an under-diagnosed and under-recognized entity. Correct identification of this distressing problem and its associated factors can lead to better management of it and improve quality of life of CKD patients.

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Conflicts of interest: None declared.

Table 1: Distribution of demographic variables among patients with or without RLS

Demographic variables	RLS Present (n=48) (%)	RLS Absent (n=158) (%)	Total (n=206) (%)	P value
Age groups (years)				
<30 yrs	6 (22.2%)	21 (77.8%)	27 (13.1%)	0.96
30-60 yrs	33 (23.9%)	105 (76.1%)	138 (67%)	
>60 yrs	9 (22%)	32 (78%)	41 (19.9%)	
Gender				
Male	25(12.14%)	118(57.28%)	143 (69.4%)	0.003
Female	23(11.17%)	40(19.42%)	63 (30.6%)	

Figures in parenthesis in column 2 and 3 represent the row percentage. Figures in parenthesis in column 4 represent the column percentage.

Table 2: Distribution of RLS among all CKD patients

RLS status	Frequency (%)
No RLS	158 (76.7%)
Have RLS	48 (23.3%)
i. Mild RLS	4 (1.9%)
ii. Moderate RLS	15 (7.3%)
iii. Severe RLS	18 (8.7%)
iv. Very severe RLS	11 (5.3%)
Total	206 (100%)

Table 3: Distribution of co-morbidities/ habitual history among patients with or without RLS

Co-morbidities/habitual history	RLS Present (n=48) (%)	RLS Absent (n=158) (%)	Total (n=206) (%)	P value	
HTN	Present	28 (23%)	94(77%)	122(59.22%)	0.88
	Absent	20 (23.8%)	64(76.2%)		
DM	Present	10(27%)	27(73%)	37(17.96%)	0.35
	Absent	38(22.5%)	131(77.5%)		
IHD	Present	5(25%)	15(75%)	20(9.71%)	0.85
	Absent	43(23.1%)	143(76.9%)		
Alcohol intake	Present	8(3.88%)	42(20.39%)	50(24.27%)	0.14
	Absent	40(19.42%)	114(55.34%)		

Figures in parenthesis in column 2 and 3 represent the row percentage. Figures in parenthesis in column 4 represent the column percentage.

Table 4: Distribution of maintenance dialysis in patients with RLS

Maintenance Hemodialysis (HD)	RLS Present (n=48) (%)	RLS Absent (n=158)(%)	Total (n=206)(%)	P value
Present (on HD)	34(35.4%)	62(64.6%)	96(46.6%)	0.001
Absent (not on HD)	14(12.7%)	96(87.3%)	110(53.4%)	

Figures in parenthesis in column 2 and 3 represent the row percentage. Figures in parenthesis in column 4 represent the column percentage.

Table 5: Association of laboratory parameters with RLS status

Laboratory Parameters	RLS Status	N	Mean	Standard Deviation	Standard Error Mean	t-value	P-value
Sr.Creatinine	RLS Absent	158	8.80	5.59	0.45	0.27	0.78
	RLS Present	48	9.05	5.09	0.73		
Blood Urea	RLS Absent	158	170.81	106.71	8.48	0.10	0.91
	RLS Present	48	168.97	108.20	15.61		
Sr. Sodium	RLS Absent	158	129.76	15.04	1.19	0.16	0.87
	RLS Present	48	129.39	8.07	1.16		
Sr. Potassium	RLS Absent	158	4.46	0.95	0.07	1.03	0.30
	RLS Present	48	4.63	1.12	0.16		
Sr. Albumin	RLS Absent	157	3.26	0.62	0.05	0.68	0.49
	RLS Present	48	3.19	0.44	0.06		
	RLS Present	48	7.16	1.94	0.28		
	RLS Present	48	73.4	11.94	1.72		

Sr. Calcium	RLS Absent	158	8.28	4.98	0.39	0.35	0.73
	RLS Present	48	8.03	1.28	0.18		
Sr. Phosphate	RLS Absent	158	5.92	2.19	0.17	0.64	0.52
	RLS Present	48	5.70	1.76	0.25		
Sr. Ferritin	RLS Absent	158	496.65	506.57	40.42	4.55	0.001
	RLS Present	48	157	177.2	25.58		

N= number of CKD patients

References

- Ojo A. Addressing the global burden of chronic kidney disease through clinical and translational research. *Trans Am Clin Climatol Assoc.* 2014;125:229-43; discussion 43-6.
- Singh AK, Farag YM, Mittal BV, Subramanian KK, Reddy SR, Acharya VN, et al. Epidemiology and risk factors of chronic kidney disease in India - results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. *BMC Nephrol.* 2013;14:114.
- Ekbom K, Ulfberg J. Restless legs syndrome. *J Intern Med.* 2009 Nov;266(5):419-31.
- Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. *Am J Kidney Dis.* 1995 Nov;26(5):751-6.
- Mucsi I, Molnar MZ, Ambrus C, Szeifert L, Kovacs AZ, Zoller R, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2005 Mar;20(3):571-7.
- Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis.* 1996 Sep;28(3):372-8.
- Kawauchi A, Inoue Y, Hashimoto T, Tachibana N, Shirakawa S, Mizutani Y, et al. Restless legs syndrome in hemodialysis patients: health-related quality of life and laboratory data analysis. *Clin Nephrol.* 2006 Dec;66(6):440-6.
- Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, et al. Restless legs syndrome in end-stage renal disease. *Sleep Med.* 2004 May;5(3):309-15.
- Bhowmik D, Bhatia M, Gupta S, Agarwal SK, Tiwari SC, Dash SC. Restless legs syndrome in hemodialysis patients in India: a case controlled study. *Sleep Med.* 2003 Mar;4(2):143-6.
- Yeh P, Walters AS, Tsuang JW. Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. *Sleep Breath.* 2012 Dec;16(4):987-1007.
- Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med Rev.* 2012 Aug;16(4):283-95.
- Patrick LR. Restless legs syndrome: pathophysiology and the role of iron and folate. *Altern Med Rev.* 2007 Jun;12(2):101-12.
- Szentkiralyi A, Molnar MZ, Czira ME, Deak G, Lindner AV, Szeifert L, et al. Association between restless legs syndrome and depression in patients with chronic kidney disease. *J Psychosom Res.* 2009 Aug;67(2):173-80.
- Gholamrezaei A, Amra B, Mortazavi M. Cardiovascular risk and mortality in end-stage renal disease patients with restless legs syndrome; need for further investigation and looking for underlying mechanisms. *Sleep Med.* 2013 Apr;14(4):385-6.
- Walters AS, Rye DB. Evidence continues to mount on the relationship of restless legs syndrome/ periodic limb movements in sleep to hypertension, cardiovascular disease, and stroke. *Sleep.* 2010 Mar;33(3):287.
- K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002 Feb;39(2 Suppl 1):S1-266.
- Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003 Mar;4(2):121-32.
- Lee J, Nicholl DD, Ahmed SB, Loewen AH, Hemmelgarn BR, Beecroft JM, et al. The prevalence of restless legs syndrome across the full spectrum of kidney disease. *J Clin Sleep Med.* 2013 May 15;9(5):455-9.
- Kavanagh D, Siddiqui S, Geddes CC. Restless legs syndrome in patients on dialysis. *Am J Kidney Dis.* 2004 May;43(5):763-71.
- Salman SM. Restless legs syndrome in patients on hemodialysis. *Saudi J Kidney Dis Transpl.* 2011 Mar;22(2):368-72.
- Allen RP, Ritchie SY. Clinical efficacy of ropinirole for restless legs syndrome is not affected by age at symptom onset. *Sleep medicine.* 2008 Dec;9(8):899-902.
- Chavoshi F, Einollahi B, Sadeghnia Haghghi K, Saraei M, Izadianmehr N. Prevalence and sleep related disorders of restless leg syndrome in hemodialysis patients. *Nephrourol Mon.* 2015 Mar;7(2):e24611.
- Araujo SM, de Bruin VM, Nepomuceno LA, Maximo ML, Daher Ede F, Correia Ferrer DP, et al. Restless legs syndrome in end-stage renal disease: Clinical characteristics and associated comorbidities. *Sleep Med.* 2010 Sep;11(8):785-90.
- Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med.* 2004 Jan 26;164(2):196-202.
- Collado-Seidel V, Kohnen R, Samtleben W, Hillebrand GF, Oertel WH, Trenkwalder C. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. *Am J Kidney Dis.* 1998 Feb;31(2):324-8.
- Riar SK, Leu RM, Turner-Green TC, Rye DB, Kendrick-Allwood SR, McCracken C, et al. Restless legs syndrome in children with chronic kidney disease. *Pediatr Nephrol.* 2013 May;28(5):773-95.
- Neves PD, Gracioli FG, Oliveira IB, Bridi RA, Moyses RM, Elias RM. Effect of Mineral and Bone Metabolism on Restless Legs Syndrome in Hemodialysis Patients. *J Clin Sleep Med.* 2017 Jan 15;13(1):89-94.
- Roger SD, Harris DC, Stewart JH. Possible relation between restless legs and anaemia in renal dialysis patients. *Lancet.* 1991 Jun 22;337(8756):1551.
- O'Keefe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing.* 1994 May;23(3):200-3.
- Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology.* 2000 Apr 25;54(8):1698-700.
- Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. *Mov Disord.* 2009 Jul 30;24(10):1445-52.
- Buchfuhrer MJ. Strategies for the treatment of restless legs syndrome. *Neurotherapeutics.* 2012 Oct;9(4):776-90.
- Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. *Am Fam Physician.* 2008 Jul 15;78(2):235-40.