

Prevalence of Restless Legs Syndrome in Haemodialysis Patients

Rashid Ahmed Shaikh, Shamsuddin Solangi, Suresh Kumar Rathi, Qurban Hussain Shaikh

ABSTRACT

OBJECTIVE: To observe the frequency and various risk factors associated with restless legs syndrome (RLS) in haemodialysis (HD) patients and to evaluate various factors associated with RLS.

DESIGN OF THE STUDY: Cross-sectional study.

PLACE & DURATION: Department of Nephrology, dialysis unit, Isra University Hospital and Hirani Dialysis Centre, Hyderabad. Duration from 15-5-2011 to 27-7-2012.

METHODS: The criteria of the international restless study group used to diagnose RLS, while John Hopkins restless legs 4 points severity scale was used to assess severity of RLS. All patients were reinterviewed and clinically examined by qualified neurologist. In this study 100 patients were included from two dialysis centre. The following data were collected: age, sex, duration of dialysis, cause of end stage renal failure, BUN, creatinin, serum sodium, serum potassium, serum calcium, serum phosphates, Hemoglobin, ferritin, albumin, and PTH level.

RESULTS: The clinical and biochemical data of 100 patients from 137 were available. RLS was present in 32 patients (32%). Mild 16 (50%), moderate 12 (37.5%) and severe R.L.S was present in 4 (12.5%) patients respectively. We found association with increasing duration of dialysis and high calcium.

CONCLUSION: The frequency of R.L.S in our dialysis patients is 32%. Results showed RLS is associated with increasing duration of dialysis and high calcium. More studies are required to see association of RLS with other factors like female gender, diabetes, and low iron.

KEY WORDS: Restless legs syndrome, haemodialysis, prevalence, calcium.

INTRODUCTION

Restless syndrome (RLS) is "characterized by a distressing irresistible urge to move the legs that is brought on by rest (sitting or lying down)" ⁽¹⁾. It is sensorimotor disorder that has profound effect on sleep ⁽²⁾. Patients may use a variety of terms to describe the sensations such as "Creepy-Crawly legs" and others. It is relieved by movement and by continued movement such as walking.

Review of literature showed that, among general population aged 65 years or older, prevalence of RLS is highly variable ranging from 5.5% ⁽³⁾, to 9.8%. While it ranges from 12.2 to 34.2% in Haemodialysis patients ^(6, 7, 8). These figures indicates that RLS is not only commonest but also most uncomfortable disorder for patients on HD. Regarding causes of RLS, familial inheritance, deficiency of iron, and abnormalities of the dopaminergic system in the central nervous system have been proposed ⁽⁹⁾. A familial inheritance for RLS supported by observation that 50% of patients with RLS have a first relative affected by syndrome ⁽¹⁰⁻¹⁴⁾.

The involvement of dopaminergic system is supported by the fact: 1) most symptoms respond to treatment with dopaminergic agents and 2) dopamine receptor antagonists that cross blood brain barrier exacerbate

the symptoms. On the other hand cause(s) of RLS in patients having haemodialysis is still obscured ⁽¹⁵⁾. The results of a large prospective study with 6 years of follow-up showed that greater the risk of developing depression, higher is the risk of developing RLS ⁽¹⁶⁾. Rationale was see the RLS in HD patients.

HD patients having RLS, the parathyroid hormones (PTH) found significantly lower and serum phosphate may be higher in comparison to those patients on HD but having no RLS ^(6, 8). Other studies found no significant difference of PTH and serum phosphate levels in these patients ⁽¹⁷⁾. There is improvement in symptoms of RLS, after iron supplements in patients with low serum ferritin levels ^(18, 19). Frequent blood donation is also presumed to be associated with RLS but no association is found in one study ⁽²⁰⁾.

PATIENTS AND METHODS

The patients after having written consents enrolled in this study. These were from two dialysis centre. Isra University Hospital dialysis centre and Hirani dialysis centre at Hyderabad. Patients were taken from both sexes of any age. Those patients were on dialysis for less than 3 months excluded from this study (n = 21). Those patients having symptoms mimic to RLS before start of dialysis were excluded from this study (n=21). The detailed history, examination and relevant investi-

gations were done of each patient.

The criteria of "The International Restless Legs Study Group" (2) was used to diagnose RLS. The diagnosis of RLS is based on following 4 criteria:

- 1). A desire to move the limbs often associated with paresthesias or dysesthesias.
- 2). Symptoms by activity.
- 3). Motor restless, and
- 4). Nocturnal worsening of symptoms.

All patients were interviewed and clinically examined by a qualified neurologist. The severity of RLS was assessed by, 4 points "John Hopkins" restless legs severity scale (21). Rating were (0) none, (1) Mild-when symptoms are during sleep period or at bed time. Symptoms may occur within 60 minutes before the usual bedtime or simply at the time of going to bed or during the night after in bed (2) Symptoms occur in the evenings (after 6pm). These may start at any time between 6pm and the usual bedtime. (3) Symptoms may start in the afternoon or may be present whole day. The data for each patients was collected, including age, gender, duration of dialysis, weekly erythropoietin dose, weekly intravenous iron dose, pre dialysis haemoglobin (Mean of 3 months) ferritin, blood urea, serum creatinin, serum sodium, serum potassium, total calcium (corrected for albumin, phosphate), intact parathyroid hormone (PTH) . Urea reduction ratio (URR) was calculated according to standard methods. The data of patients with and without RLS was compared.

Statistical analysis

The data was analysed result is presented in terms of frequency, percentage mean with standard deviation of qualitative type of data. The Mann-Whitney U-test the Chi-square test was used for statistical analyses; p < 0.05 was considered statistically significant.

RESULTS

Total number of patients were 137 who were on regular Haemodialysis for more than 3 months at either dialysis centre were approached at the time of the study, and other 100 patients participated in this study, 55 were male (55%) and female 45 (45%), age ranged from 10 to 70 years. (Mean = 45.06). In our study RLS was present in 32 patients (prevalence 32%), including 18 males and 14 females. 16 (50%) of the 32 patients with RLS had mild, 12 (37.5%) had moderate and 4 patients had severe RLS (12.5%). The clinical data of patients with and without RLS are shown in table I.

It shows that patients having more duration of dialysis have more prevalence of RLS. Age, female gender and any particular cause of ESRD, particularly diabetes showed no significance. The laboratory data are

shown in table 2, RSL group serum calcium was significantly higher, while no significant difference of intact PTH, serum phosphate, and ferritin was seen in both groups.

TABLE I: CLINICAL DATA OF PATIENTS WITH AND WITHOUT RLS

	RLS (n = 32)	NON RLS (n=68)	P VALUE
Mean age (years)	45.06±9.01	46.60±12.20	> 0.05 N.S
Male	18/32	37/68	> 0.05 N.S
Female	14/32	31/38	> 0.05 N.S
Mean duration of HD (Months)	27.72±6.93	21.75±5.18	0.0001**
Primary cause (Disease)			
Diabetic Nephrology	16 (50%)	32 (47%)	> 0.05 N.S
Hypertension	9 (28.11%)	23 (33.8%)	> 0.05 N.S
Chronic Glomerulonephritis	4 (12.5%)	8 (11.76%)	> 0.05 N.S
Renal stone disease	3 (9.39%)	5 (7.35%)	> 0.05 N.S

TABLE II: LABORATORY DATA OF PATIENTS WITH AND WITHOUT RLS (MEAN ± SD)

	RLS	Non-RLS	P Value
Hemoglobin g/dl	9.14±1.90	9.11±2.14	> 0.05 N.S
Ferritin ng/ml	252±1.90	234 ± 191	> 0.05 N.S
Serum creatinine mg/dl	10.23±2.62	10.40±2.255	> 0.05 N.S
Blood urea nitrogen (mg/dl)	69.3 ± 15.1	69.2 ± 15.2	> 0.05 N.S
Serum sodium (mmol/L)	135.88±4.38	136.79±5.87	> 0.05 N.S
Serum Potassium	4.28 ± 0.54	4.29 ± 0.52	> 0.05 N.S
Serum Phosphate (mg/dl)	5.37 ± 1.14	5.40 ± 1.11	> 0.05 N.S
Serum Calcium (mg/dl)	9.07 ± 0.86	8.49 ± 0.88	<0.0003 **
Intact parathyroid hormone (Pg/ml)	315 ± 188	321 ± 194	> 0.05 N.S
Serum Albumin (g/dl)	3.76 ± 0.52	3.83 ±0.99	> 0.05 N.S

NS = Non Significant

DISCUSSION

Although RLS has been addressed in general population but so far no study has been done for RLS in Haemodialysis (HD) patients in Pakistan. Therefore this is the first study that has been discussed the RLS in Haemodialysis patients. It shows that RLS in Pakistan is under recognized, misdiagnosed and maltreated⁽²²⁾. The result of this study showed that frequency of RLS in HD patients is 32% which is significant. However it shows considerable variation in different part of the world and is reported between 12.2 to 34.2%^(6, 7, 8) in different international studies. In dialysis patients diagnosis of RLS is important because it cause significant disturbance to many patients^(20, 24) and in order to diagnose there is world wide well accepted criteria of "the International Restless Legs Study Group".

We observed in our study that increasing duration of dialysis and increased levels of serum calcium were independently associated with RLS. The three other studies have same observations regarding association between RLS and increasing duration of dialysis^(25, 26, 27). But other studies have not supported these findings^(28, 29, 30). This may be because of low prevalence of RLS in these studies. One might speculate the accumulation in dialysis related amyloid. Further studies may support this association.

The laboratory data are shown in table 2. Calcium was significantly higher in RLS group then in Non RLS groups, while the other data did not differ significantly. The higher calcium was also seen in patients on dialysis patients^(27, 30) and correction with erythropoietin and iron shown improvement⁽²⁷⁾ in our study including other studies failed to shown association of anemia with RLS^(28, 29). In contrast to previous studies, our study did not show any association of RLS with diabetes,⁽²⁴⁾ increased phosphate⁽³⁰⁾ and increased PTH levels⁽¹⁹⁾. There was not shown females having higher prevalence of RLS in our study, in contrast to several other studies.^(25, 32, 33)

CONCLUSION

RLS is common in haemodialysis patients and it is more frequent in patients having prolonged duration of dialysis and high calcium level. More studies are needed for association of other factors like gender, deficiency increased body weight, further attention that may lead to better understanding of RLS.

REFERENCE

1. Allen RP, Piechietti D, Henning WA et al. Restless legs syndrome: diagnostic criteria special considerations, and epidemiology workshop at the national institute of health sleep Med 2003; 4:101-19.
2. Allen RP, Earley CJ. Validation of the Johns Hopkins Restless Legs Severity Scale (JHRLSS). Sleep Med. 2001; 2:239-242.
3. Earley CJ. Restless legs. Syndrome N Engl J Med. 2003; 348: 2013-2019.
4. Earley CJ. Clinical practice: Restless legs syndrome N Engl J Med 2003; 348:2013-9
5. Walter AS. Towards a better definition of the restless legs syndrome. The International Restless Syndrome Study Group. Mov Disord. 1995; 10 : 364 - 642.
6. Ohayon M M, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. Psychosom Res. 2002; 53: 549-554.
7. Rothdach AJ, Trenkwalder C, Haberstock J. Prevalence and risk factors of RLS in any elderly population: the MEMO study: Memory and Mobility in Augsburg Elderly. Neurology. 2000; 54: 1064 -1068.
8. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord. 2001; 16: 1159-1163.
9. Collado-Seidel V, Kohnen R, Santleben W. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. Am J Kidney Dis. 1998; 31: 324-328.
10. Huiqi Q, Shan L, Mingcai Q, Restless leg syndrome (RLS) in uremic patients is related to the Frequency of hemodialysis sessions. Nephron. 2000; 86: 540.
11. Takaki. J, Nishi T, Nangaku M. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. AM J Kidney Dis. 2003; 41: 833-839.
12. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol. 2001; 18: 128-1747.
13. Jessica E. young SBC, CarleVilarino-Geol, PhD. Clinical and Genetic Description of a family with high prevalence of Autosomal Dominant Restless legs Syndrome. Mayo Clin Proc. Feb 2009;84(2): 134-138.
14. Ondo W, Jankovic J. Restless legs syndrome. Clinicopathologic correlates. Neurology. 1996; 47: 1435-1441.
15. Walters AS, Hickey K, Malzman J, et al. A questionnaire study of 138 patients with restless legs syndrome: the "Night-Walkers" every survey. Neurology. 1996; 46:92-95.
16. Montplaisir J, Coucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients

- diagnosed with new standard criteria. *Mov Disord*. 1997; 12: 61-65.
17. Hening WA, Washburn M, Allen RP, Lesage S, Earley CJ, Blinded diagnoses confirm elevated frequency in relatives of restless legs syndrome (RLS) probands in a casecontrol family study of RLS. *Mov Disord*, 2004; 19 (suppl): S363.
 18. Kawauchi A, Inoue Y, Hashimoto T, et al. Restless Legs Syndrome in hemodialysis patients: Health-related quality of life and laboratory data analysis. *Clin Neph*, volume 66, 2006; No. 6: 440-446.
 19. Yanping Li, Fariba Mirzaei, Eilis J. O'Reilly, et al. Prospective study of Restless Legs Syndrome and Risk of Depression in Women. *Am J Epidemiol*, 2012;176(4):279-88.
 20. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep*. 1998; 21: 371-377.
 21. Sloan JA, Shelly MA, Feinging A, Bernstein P, Monk RD. double-blind, Placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis*. 2004; 43: 663-670.
 22. Salas RE, Gamaldo CE, Allen RP. Updates in restless legs syndrome. *Curr Opin Neurol* 2010; 23(4):401 – 406.
 23. Arunthari V, Kaplan J, Fredrickson PA, Lin S, Castillo PR, Hechman MG. Prevalence of restless legs syndrome in blood donors.. *Mov Disord*. 2010 Jul 30; 25(10): 1451-5.
 24. Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. *Sleep Med*. 2001; 2: 239:241.
 25. Chaudhry A, Malik K, Ahmed J. *Ann king Edward Med Coll Sep* 2005; 11(3): 271-2.
 26. Kavanagh D, Siddiqui S, Geddes CC: Restless legs syndrome in patients on dialysis. *Am J Kidney Dis* 2004; 43: 763-771.
 27. Unruh MI, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB: Restless legs syndrome among patients on dialysis: association with lower quality of life and shorter survive. *Am J Kidney Dis* 2004; 43: 900-909.
 28. Siddiqui S, David K, Jamie T, May M, Christopher D, *Clin Pract* 2005; 101:c155-c160.
 29. Gigli GL, Adorati M, Doslo P, Piani A, Valente M, Brotini S, Budai R: Restless legs syndrome in end-stage renal disease. *Sleep Med* 2004; 5: 309-315.
 30. Roger SD, Harris DC, Stewart JH: Possible relation between restless legs and anaemia in renal dialysis patients. *Lancet* 1991; 337:1551.
 31. Collado-Seidel V, Kohnen R, Samtleben W, Hilebrand GF, Oertel WH, Trenkwalder C: Clinical and biochemical findings in uremic patients with and without restless legs syndrome. *Am J Kidney Dis* 1998; 31: 324-328.
 32. Miranda M, Araya F, Castillo JL, Duran C, Gonzalez F, Aris L: Restless legs syndrome: a clinical study in adult general population and uremic patients. *Rev med Chil* 2001; 129: 179-186.
 33. Takaki J, Nishi T, Nangaka M, Shimoyama H, Inada T, Matsuyama N, Kumano H, Kuboki T: Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. *Am J Kidney Dis* 2003; 41: 833-739.
 34. A. Kawauchi, Y. Inoue, T. Hashimoto, N. Tachinana, S. Shirakawa, Y. Mizutani, T. Ono, T. Miki. Restless legs syndrome in hemodialysis patients: health-related quality of life and laboratory data analysis. *Clin Nephrology*, Vol. 66-No. 6: 2006; 440-446.
 35. Berger K, Lucdemann J, Trenkwalder C, John U, Kessler C: Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med* 2004; 164: 196-202.
 36. Gao X, Schwarzschild MA, Wang H, et al. Obesity and restless legs syndrome in men and women. *Neurology*.2009; 72(14):1225-1261.



AUTHOR AFFILIATION:

Dr. Rashid Ahmed Shaikh (*Corresponding Author*)

Department of Nephrology
Isra University Hospital Hyderabad, Sindh-Pakistan.
Email: prof.shaikh@yahoo.com

Dr. Shamsuddin Solangi

Assistant Professor, Department of Medicine
Isra University Hospital Hyderabad, Sindh-Pakistan.

Dr. Suresh Kumar Rathi

Associate Professor, Department of Medicine
Isra University Hospital Hyderabad, Sindh-Pakistan.

Dr. Qurban Hussain Shaikh

Registrar, Medicine of Department
Jinnah Postgraduate Medical Centre
Karachi, Sindh-Pakistan.