

Association of Restless Leg Syndrome with Iron Deficiency Anaemia

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ABSTRACT

Background: Iron deficiency anaemia (IDA) and rest leg syndrome (RLS) are two common medical conditions in our population. There is etiologic association between the two pathologies which however; has not been investigated in our local population.

Objective: To determine the frequency of iron deficiency anemia among patients of restless leg syndrome.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Neurology, Khairpur Medical College- Khairpur Mir's from December 2020 to March 2021.

Methodology: Three hundred and thirty nine patients having RLS, of either gender, age 18-60 years, were included after taking a valid informed/written consent. Pregnant women or having menorrhagia, blood dyscrasias, iron supplements or steroids, any neurological comorbid or comatose patients were excluded.

Results: The mean age was 39.12 ± 10.79 years. The mean duration of RLS was 8.42 ± 4.01 years while mean haemoglobin was 12.06 ± 2.36 g/dL. The prevalence of IDA among RLS patients was 133 (39.2%). The stratified analysis significantly revealed that elder age, female gender, positive family history, and higher BMI were associated with increased frequency and severity of IDA among RLS patients ($P=0.996, 0.007, 0.372$ & 0.738).

Conclusion: Iron deficiency anaemia is quite frequent in patients of Restless leg syndrome and healthcare providers should increase awareness among population regarding its treatment.

Key words: Restless leg syndrome, Iron deficiency, Anaemia, Haemoglobin, Sleep disturbance

INTRODUCTION

Restless legs syndrome (RLS) also known as Willis–Ekbom disease is a common, but underdiagnosed clinical syndrome that affects approximately upto 15% of population.¹ Urgency to move the legs associated with unpleasant sensations in the lower limbs are characteristic symptoms of RLS which are relieved by continuously moving limbs. It is a treatable condition is caused by certain factors including genetic predisposition/inheritance, neurological lesions, uremia, pregnancy, drug side effects however; iron deficiency is probable the most common of these.^{2,3} Any age may be affected but usually found in elder age.⁴ Restless legs syndrome is identified by the following tetrad of symptoms: focal akathisia (an irresistible desire to move localized to the extremities that is periodic and distressing due to abnormal sensations), motor restlessness, quiescagenic symptoms (engendered or exacerbated by remaining at rest), and circadian phenomenon (symptoms worsen in the evening/night for a person entraining to a normal circadian rhythm).⁵

Restless legs syndrome affects the quality of life of people by affecting social activities, family life and occupations which may lead to loss of job. Sleep disturbance is also common with RLS thus; the condition hampers the ability live a satisfied and joyful life.⁶ Restless legs syndrome almost never resolves on its own and needs treatment. However; there is a little research conducted on etiologic factors of RLS and effectiveness of different treatment modalities in local population.⁷

Malnutrition due to poor nutrition and poverty are quite common in our country. Iron deficiency leads to many symptoms of which most prevalent is microcytic hypochromic anaemia. However; there are many other

specifically neurological manifestations which are common yet overlooked in daily medical practice. One such very common yet least studied clinical feature associated with IDA is restless leg syndrome.⁸ The precise pathophysiologic mechanism of iron metabolism plays in bringing about the disease in brain is yet debated in scientific community.⁹ It has been found that approximately 31% patients having IDA develop RLS with whereas the rest of the population is resistant to developing RLS even with significant IDA.¹⁰ A study found that 76% patients with IDA became free from symptoms of RLS when they were treated with 1,000 mg IV of Iron dextran.¹¹⁻¹³

The objective of this study is to determine the frequency of iron deficiency anemia among patients of restless leg syndrome presenting to a tertiary care setup and to investigate other associated risk factors and demographic and clinical patterns of the disease among local population. The results of this study will document the evidence as well as raise awareness of this condition and its treatment at improving QoL of such patients.

MATERIALS AND METHODS

A cross sectional study on patients with RLS [confirmed through International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria] at the neurology OPD was conducted in a period of three months after approval from the research evaluation committee Ethical Review committee of Khairpur Medical College Khairpur Mir's. Patients of either gender, age 18-60 years, non-surgical, were included after taking a valid informed/written consent. Pregnant women or having menorrhagia, blood dyscrasias, iron supplements or steroids, any neurological comorbid or comatose patients,

mentally handicapped persons were excluded. A total of 339 RLS patients were enrolled. Iron deficiency anemia [defined as having anemia Hb<12 gm/dL in males and <11 gm/dL in females and iron deficiency (free erythrocyte protoporphyrin (FEP) >100 µg/dL, and serum total iron binding capacity (TIBC) >360 µmol/L] were noted on the patients.

Data on demographic variables, (age, gender, residence) were collected along with the disease related variables (study variables) like type, location, duration and severity of restless leg among patients were noted. Outcome variable was presence of IDA confirmed through Hb% level, serum Free Erythrocyte Protoporphyrin (FEP), total iron-binding capacity (TIBC), bilirubin level and serum urea level. Presence of comorbid like uremia was deemed as effect modifier.

Data analysis and presentation was done through SPSS-25. To evaluate the effect modification, study variables were stratified followed by application of chi-square with a p value <0.05 taken as significant. Further advance statistical test and correlation was also evaluated.

RESULTS

The current study was undertaken as part of a randomized clinical trial. Total 339 patients were included as sample which presented to neurology department with complaints of restless leg syndrome (RLS). Their mean age was 39.12±10.79 years. The duration of RLS ranged from 01 to 15 days with a mean of 8.42±4.01 years. The mean haemoglobin was 12.06±2.36 g/dL ranged from 6.1 to 16.5 g/dL (Table 1). The mean total iron-binding capacity was 37.05±32.01 µmol/L (range: 11-123 µmol/L).

The prevalence of iron deficiency anaemia (IDA) among RLS patients was 133 (39.2%). Mild anaemia was detected in 79 (13.3%) patients of RLS followed by moderate anaemia in 41 (12.1%) while severe anaemia affected 13 (3.8%) patients of RLS (Fig. 1). Table 2 showed the stratified analysis which significantly revealed that among IDA affected mild and moderate anaemia was on higher side among female gender as well as the frequency of IDA overall was also more in female patients (P=0.007). Further it was noted that increase in age was associated with an increase in frequency of anemia of all levels among RLS patients however; severe anaemia was more prevalent (P=0.996). Additionally; having a family member affected of RLS was associated with increased frequency of anemia among RLS patients (P=0.372).

Finally; it was noted that body mass index was also an effect modifier and it slimmer underweight patients has higher frequency of anemia of all levels among RLS patients however; the finding lack statistical significance. Comparison of rural-urban residence showed that living in rural areas were associated with slightly higher frequency of IDA among RLS patients [P=0.561] (Table 3).

Table 1: Baseline demographic characteristics (n= 339)

Variable	Mean±SD
Age (years)	39.12±10.79
Duration of restless leg (years)	8.42±4.01
Haemoglobin (g/dL)	12.061±2.36
Total iron-binding capacity (µmol/L)	37.05±32.01
Serum Ferritin (µg/dL)	67.38±49.65

Table 2: Effect of other variables on iron deficiency anaemia among patients of RLS (n = 339)

Variable	Severity of iron deficiency anaemia				P value
	Mild	Moderate	Severe	Nil	
Gender					
Male	8 (2.7%)	32 (10.8%)	70 (23.7%)	185 (62.7%)	0.007
Female	5 (11.8%)	9 (20.9%)	9 (20.5%)	21 (47.7%)	
Age (years)					
18-20	-	2 (13.3%)	3 (20%)	10 (66.7%)	0.996
21-30	2 (2.3%)	12 (14%)	21 (24.4%)	51 (59.3%)	
31-40	3 (4.8%)	7 (11.3%)	13 (21%)	39 (62.9%)	
41-50	4 (3.7%)	12 (11.2%)	25 (23.4%)	66 (61.7%)	
51-60	4 (5.8%)	8 (11.6%)	17 (24.6%)	40 (58%)	
Family history of RLS					
Yes	5 (3.8%)	16 (12.2%)	37 (28.2%)	73 (55.7%)	0.372
No	8 (3.8%)	25 (12%)	42 (20.2%)	133 (63.9%)	

Table 3: Effect of other variables on iron deficiency anaemia among patients of RLS (n=339)

Variable	Severity of iron deficiency anaemia				P value
	Mild	Moderate	Severe	Nil	
Body mass index					
Under weight	2 (14.3%)	1 (7.1%)	2 (28.6%)	7 (50%)	0.738
Normal weight	2 (2%)	14 (14.3%)	21 (21.4%)	61 (62.2%)	
Over weight	6 (4.1%)	14 (9.6%)	38 (26%)	88 (60.3%)	
Obese	3 (4%)	11 (14.7%)	15 (20%)	46 (61.3%)	
Very obese	-	1 (16.7%)	1 (16.7%)	4 (66.7%)	
Residence					
Rural	11 (4.8%)	26 (11.4%)	53 (23.1%)	139 (60.7%)	0.561
Urban	2 (1.8%)	15 (13.6%)	26 (23.6%)	67 (60.9%)	



Fig. 1: Frequency and severity of iron deficiency anaemia among patients of restless leg syndrome (n = 339)

DISCUSSION

Iron deficiency anaemia (IDA) is very common medical condition. It may be a cause as well as may occur as a comorbid with many illnesses. Many times relation of IDA with other illness seems irrelevant or trivial- but indeed has a great impact. As a common finding of our daily neurological practice, it was observed that rest leg syndrome is quite common yet; ignored by the healthcare providers and the patients. A restless leg is a treatable and socially non-accepted activity. The current study focused to investigate connection between two commonly found pathologies i-e; RLS with IDA.

The current study found that prevalence of IDA among RLS patients was 39.2%. A study from Sao Paulo

found that only 5% of RLS patients had IDA associated while on the other extreme a studies by Daubian-Nose et al¹⁴ Weinstock and Walters¹⁵ found that 43% RLS patients had IDA. Allen et al¹⁰ noted that one third of patients (31%) have IDA with RLS. A study from Saudi Arab noted that IDA was present in 57% patients of secondary RLS.⁸ Thus; the single most consistent finding and the strongest environmental risk factor associated with RLS is IDA.

Gender wise bifurcation showed that female RLS patients were more affected from IDA than their counterparts (i.e. 52.4% vs 37.3%; p value = 0.007). Although the female patients were less than males overall; yet they had higher IDA prevalence. It is also important to note here that cases of moderate and mild anaemia were more in female patients. This reflects condition of females in our far reached areas. Iron deficiency is as highly prevalent as 25-75% even in non-pregnant, non-lactating females in various parts of country.¹⁶ Curgunlu et al¹⁷ reported that occurrence and severity of RLS is more common in women than in men. It may get worse or even appear first time in pregnant women.^{18,19} Contrary to this a study from Saudi Arab found that male gender is more affected by primary RLS (OR = 14.53, 95% CI [2.9-75], P = 0.001).⁸

In current study, mean haemoglobin of those having IDA was 9.03±1.43 g/dL [Males 9.15±1.39 & females 8.47±1.51 g/dL] while those diagnosed as not having IDA; mean haemoglobin was 13.51±1.31 g/dL [males 13.61±1.31 and females 12.61±0.987 g/dL]. We noted that anaemia varied in severity and more cases were of mild anaemia (13.3%) followed by moderate and severe anaemia (12.1% and 3.8% respectively) among all patients of RLS.

The mean age of patients was 39.12±10.79 (18 to 60 years) which includes the women of reproductive age. This may be one reason that women had presented with higher number of IDA patients. Overall however; almost half of patients were of age below 40 years while others were of age between 41-60 years. Other studies have also found resembling age distribution of RLS. A study from Brazil noted that mean age of RLS patients was 52.4±16.4 years.¹ Allen et al¹⁰ in their study found the mean age of RLS patients was 45.6 ± 18 years. A study from Saudi Arab noted that mean age of patients was 44 years.⁸ Another study denoted that average age of women RLS patients was 34.35±9.9 years while that of men was 45.8±9.0 years.²⁰ The RLS is more common in older ages, which is similar to the above findings.^{6-9,12,15}

Hereditary transmission plays significant role in RLS as many reliable studies have demonstrated that 50% of RLS patients have a positive family history.^{21,22} In current study there were about 38.6% patients of RLS had positive family history (P=0.996). Mainly affected were parents followed by offspring and siblings. Other studies have worked in details where genetic polymorphism of the five genes variants (MEIS1, BTBD9, MAP2K5, LBXCOR1 and PTPRD) in addition, the gene BTBD9 in humans, have been associated with restless legs syndrome and serum ferritin^{7,9,14,23} however; were beyond the scope of this study. We recommend that in our population such studies should be carried out.

Another risk factor was body mass index evaluated for relationship of RLS with IDA.¹⁰⁻¹⁵ It was noted that patients with lower BMI (underweight) RLS patients were more affected of IDA and in them even severe anaemia was more compared to others (P=0.738). This finding corresponds with our national statistics wherein physically under nutrition is still much prevalent which makes people prone to anaemia. On the other hand it is also worth noting that even patients with normal weight had quite high proportion of severe anaemia. Other studies also noted similar findings i.e. the mean body mass index of RLS patients was 26.5±5.5 kg/m².^{1,24}

Sleep disturbance is very much common among patients of restless leg syndrome or some call both as same thing.^{8,17,18} In current study >58% patients of RLS said having sleep difficulty. It is a common perceptions that population living in rural areas of developing countries like Pakistan continue to face health and nutrition related medical problems. The majority of RLS patients in this study were from rural areas and it was found that they suffered more from mild anaemia while moderate and severe anaemia was more frequent among the urban living patients. Overall; there was only a little difference between the two groups regarding frequency of IDA (P=0.561).

Pregnant women, end stage renal disease, family history, chronic blood donors, children with ADHD and those having vitamin B12 deficiency are at significant risk of developing RLS. Professor Nordlander first recognized the association between iron deficiency and RLS, and reported that treatment of the iron deficiency markedly improved, if not eliminated, the RLS symptoms.²⁵ Our healthcare providers should consider RLS as a significant illness and increase awareness among population regarding its treatment.

CONCLUSION

Restless leg syndrome is common neurological disorder in our population. Its association with iron deficiency anaemia in well observed in other countries; same is the case with our local population. Although we come across not many women patients of RLS however; they are more affected from frequency and severity of IDA. Higher the age, and lower the BMI; the association with iron deficiency anaemia is strong. Familial tendency also is risk factor for RLS. Healthcare providers should increase awareness of RLS among patients so as to decrease the morbidity.

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