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RELATIONSHIP BETWEEN IRON DEFICIENCY ANAEMIA WITH RESTLESS LEG SYNDROME (RLS) AND SLEEP QUALITY

Psychiatry

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ABSTRACT

Aim: This study was conducted to determine the relationship between iron deficiency anaemia with restless leg syndrome and sleep quality. **Materials And Methods:** In this prospective observational study 92 consecutive patients who visited the out patients department with any sleep related complaint were invited to participate in the study. Of 92 patients, 57patients were diagnosed of restless leg syndrome (RLS) and were included in the study. Outcome variable was presence of IDA confirmed through Hb% level and total iron-binding capacity (TIBC), bilirubin level and serum urea level, Pittsburgh Sleep Quality Index (PSQI) and severity distribution of restless legs syndrome. **Results:** The mean restless legs syndrome score in anaemic patients was 16.62±6.65 with the range from 4-29, while in non-anaemic patients mean restless legs syndrome score was 10.75±6.29 with the range from 2 to 21. A significant difference was observed between anaemic and non-anaemic patients with the p value of 0.0001. In anaemic group maximum 12 (50%) patients had severe to very severe RLS, while in non-anaemic group 84.85% patients had mild to moderate RLS and only 15.15% patients had severe RLS. Mean total sleep quality score was 6.97 ± 1.92 in anaemic patients and 4.88 ± 1.57 in no-anaemic patients. In terms of total PSQI score, there was a statistically significant difference between the anaemic and non-anaemic patients, p value =0.0001. **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 and IDA affects sleep quality irrespective of co-morbid psychiatric disorders such as depression and anxiety.

KEYWORDS

Restless leg syndrome, Sleep disorder, Iron deficiency anaemia, Relation

INTRODUCTION

Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is a common neurological sensorimotor disorder often associated with severe sleep disturbances and an impaired quality of life [1]. Restless legs syndrome (RLS) is a sensory and motor disorder characterized by unpleasant sensations and pain, especially in the legs, and an irresistible urge to move them during sleep or rest. Symptoms commonly occur in the evening or at night and decrease with movement and often lead to sleep disturbance [3]. There is often an unpleasant feeling in the legs that improves temporarily by moving them [3].This feeling is often described as aching, tingling, or crawling in nature [3]. Occasionally, arms may also be affected [3]. The feelings generally happen when at rest and therefore can make it hard to sleep. Additionally, many have limb twitching during sleep, a condition known as periodic limb movement disorder [4]. RLS is not the same as habitual foot-tapping or leg-rocking [1].

The reported prevalence of RLS in the general population varies between 5% and 15% [5]. Some but not all reports suggest marked geographic differences in the prevalence of RLS with a lower prevalence in Asian countries [6]. Around 2.7% of individuals experience at least moderately distressing symptoms likely to warrant treatment, of whom 55.5% experience disturbance of daytime functioning [7]. In a US survey of RLS prevalence and burden, 1.5% of respondents were identified as RLS sufferers (symptoms ≥ 2 times per week with moderate-to-severe distress), with a mean work productivity loss of 1 day per week [8].

RLS is thought to be a central nervous system disorder related to dopaminergic dysfunction and impaired iron homeostasis in the brain [9]. Proteomic analysis of the cerebrospinal fluid of patients with RLS reveals a protein profile that is consistent with clinical findings of disruptive sleep, cardiovascular dysfunction, and painful symptoms [10]. Around 60% of patients with idiopathic/primary RLS have a first-degree relative who also suffers from the disorder, [11] and genome-wide association studies have identified genetic risk factors [12]. Secondary RLS is associated with iron deficiency, pregnancy, and end-stage renal disease; all 3 conditions are characterized by reduced central iron availability [13]. RLS prevalence increases with the progression of these diseases, and iron supplementation has been found to reduce the symptoms of RLS [14]. Both the prev alence and severity of RLS are higher in patients with IDA compared with the general population. Previous studies have reported the prevalence of RLS to be 5%–10% in the general population [15] and 25%–43% in patients with IDA [16]. The correlation between RLS severity and serum ferritin level has been well defined [13, 17]. Iron deficiency in the brain may lead to dysfunction of the striatal dopamine neurotransmission pathway, resulting in RLS [18]. Many studies were done on the general population; however, there are few studies on the relationship between iron deficiency anemia with RLS and sleep quality. In this sense, the present study was conducted to determine the relationship between iron deficiency anaemia with restless leg syndrome and sleep quality.

MATERIALS AND METHODS

This prospective observational study was conducted at postgraduate department of Psychiatry, Institute of mental health and Neurosciences (IMHANS), GMC, Srinagar from 2022 to 2023. In this study 92 consecutive patients who visited the out patients department with any sleep related complaint were invited to participate in the study. Patients of either gender, age >18 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 and mentally handicapped persons were excluded from the study. Data on demographic variables, (age, gender, residence) were collected. After a complete clinical history and physical examination, the participants were requested to answer a self-administered questionnaire survey about RLS. The questionnaire included four questions based on the essential diagnostic criteria for RLS as set by the IRLSSG in 2003 [2]. Of 92 patients, 57patients were diagnosed of restless leg syndrome (RLS) and were included in the study.

Outcome variable was presence of IDA confirmed through Hb% level and total iron-binding capacity (TIBC), bilirubin level and serum urea level, Pittsburgh Sleep Quality Index (PSQI) and severity distribution of restless legs syndrome. Presence of comorbid like uremia was deemed as effect modifier. 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.

Statistical Analysis

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

RESULTS

The mean age of patients was 34.5±7.22 (range 21-59) years. There were 18 (32%) male patients and 39 (68%) were females. The socio-demographic characteristics of the study groups are given in Table 1.

In this study, mean duration of RLS was 12.29±4.98 (range 4-35) days. The mean hemoglobin was 11.72±3.02 g/dL ranged from 6.5 to 16.2 g/dL. The mean total iron-binding capacity was 41.95±29.91 (range (range 14-119) µmol/L (Table 1).

Table 1: Baseline demographic characteristics of patients

Age (Mean ± SD)	34.5	7.22
Age group (Years)		
18-30 (No. /%)	21	37
31-45 (No. /%)	17	30
46-60 (No. /%)	12	21
>60 (No. /%)	7	12
Gender		
Male (No. /%)	18	32
Female (No. /%)	39	68
Marital status		
Unmarried (No. /%)	13	23
Married (No. /%)	44	77
Income status		
Low (No. /%)	19	33
Middle (No. /%)	27	48
High (No. /%)	11	19
Duration of RLS (Mean/range) days	12.29±4.98	4-35
Hemoglobin (Mean/range) g/dL	11.72±3.02	6.5-16.2
Total iron-binding capacity (Mean/range) µmol/L	41.95±29.91	14-119

In this study, the prevalence of iron deficiency anaemia (IDA) was 24 (42%). Mild anemia was detected in 12 (21%) patients followed by moderate anaemia in 9 (16%) while severe anaemia affected 3 (5%) patients (Fig. 1).

FIG. 1: SEVERITY OF IRON DEFICIENCY ANAEMIA

Association of Iron deficiency Anaemia with RLS

The mean restless legs syndrome score in anaemic patients was 16.62±6.65 with the range from 4-29, while in non-anaemic patients mean restless legs syndrome score was 10.75±6.29 with the range from 2 to 21. A significant difference was observed between anaemic and non-anaemic patients with the p value of 0.0001. In anaemic group maximum 12 (50%) patients had severe to very severe RLS, while in non-anaemic group 84.85% patients had mild to moderate RLS and only 15.15% patients had severe RLS (Table 2).

Table 2: Severity distribution of restless legs syndrome

Severity	Anaemic patients (N=24)		Non-anaemic patients (N=33)	
	No. of patients	Percentage	No. of patients	Percentage
Mild (0-10)	5	21.83	17	51.52
Moderate (11-20)	7	29.17	11	33.33
Severe (21)	9	37.5	5	15.15
Very severe (22-40)	3	12.5	0	0
Mean	16.62±6.65 (range 4-29)		10.75±6.29 (range 2-21)	
P Value= 00001				

Association of Iron deficiency Anaemia with quality of sleep

In this study, mean total sleep quality score was 6.97 ± 1.92 in anaemic patients and 4.88 ± 1.57 in no-anaemic patients. In terms of total PSQI score, there was a statistically significant difference between the anaemic and non-anaemic patients, p value =0.0001. The mean PSQI subscales are depicted in table 3.

Table 3: Distribution of the Pittsburgh Sleep Quality Index (PSQI) and its scales

Questionnaires	Anaemic (mean)	Non-anaemic (mean)	P Value
Subjective sleep quality	1.28 ± 0.27	0.90 ± 0.31	0.0001
Sleep latency	1.26 ± 0.22	1.02 ± 0.31	0.0001
Sleep duration	0.71 ± 0.21	0.65 ± 0.11	0.080 8
Habitual sleep efficiency	0.62 ± 0.23	0.56 ± 0.19	0.1423
Sleep disturbances	1.55 ± 0.19	1.01 ± 0.11	0.0001
Use of sleep medication	0.38 ± 0.10	0.05 ± 0.01	0.001
General dysfunction	1.31 ± 0.23	0.95 ± 0.21	0.0001
Total sleep disorder	6.97 ± 1.92	4.88 ± 1.57	0.0001

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 practice, it was observed that rest leg syndrome is quite common yet; ignored by the healthcare providers and the patients. The current study focused to investigate relation between commonly found pathologies i-e; RLS and sleep disorder with IDA.

The current study found that prevalence of IDA among RLS patients was 42%. 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 al [19], Weinstock and Walters [20] found that 43% RLS patients had IDA. Allen et al [21] 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 [22]. Thus; the single most consistent finding and the strongest environmental risk factor associated with RLS is IDA.

In a study conducted by Hyoeun Bae et al. [23] in Korea aimed at the prevalence of RLS in patients with iron deficiency anemia, 40.3% of patients had RLS, the majority (82%) of which was severe and very severe. Also, patients with iron deficiency anemia and RLS had more sleep disorders and emotional problems than patients with iron deficiency anemia without RLS.

In our study, a significant correlation was observed between iron deficiency anaemia and RLS. In this study 50% patients among anaemic had severe to very severe RLS and in non-anemic patients only 15.15% had severe RLS. Generally, although the pathophysiology of RLS is still not fully understood; however, dopaminergic system disorder, genetics, and iron deficiency have been mentioned among the causes of this disease [24, 25]. Iron is implicated in different brain physiological processes, such as dopamine production, synaptic density, myelin synthesis, and energy production, and probably in norepinephrine and serotonin neurotransmitter systems [26]. There is strong evidence linking iron deficiency to the pathophysiology of RLS, PLMD, ADHD, and RSD. The brain dopamine production system is known to play an important role in these conditions [26, 27]. Due to its ability to interconvert ferric and ferrous forms, iron is one of the core elements of oxygen transport (hemoglobin), oxygen storage (myoglobin), and energy production (cytochromes), and of the catabolism of several enzymes, such as tyrosine hydroxylase, which is the rate-limiting step in dopamine production. Iron levels are kept within physiologic ranges through feedback loops regulating iron absorption [28]. Hepcidin is known as the main regulator of iron homeostasis in gut and blood cells [29].

Iron deficiency has been described to cause behavioral and developmental symptoms [30]. Iron has a complex effect on dopaminergic function. It is a cofactor for tyrosine hydroxylase and is integral to D2 receptor function [31]. In our study a significant correlation was observed between iron deficiency and sleep disorders. In this study, mean total sleep quality score was 6.97 ± 1.92 in anaemic patients and 4.88 ± 1.57 in no-anaemic patients. Neuromodulation by the DA system plays an important role in sleep regulation, comprising the modulation of REM sleep quality, quantity, and timing [32]. Holst et al. [33] studied sleep-wake regulation in humans and combined pharmacogenetic and neurophysiologic methods to analyze the effects of the 3′-UTR variable-number-tandem-repeat polymorphism of the gene (DAT1, SLC6A3) encoding dopamine transporter. Their results recommended that the dopamine transporter contributes to homeostatic sleep-wake regulation in humans. Peirano et al. [34]

described that relative to controls, children with IDA showed longer duration of REM sleep episodes in the first third and shorter in the last third; more REM sleep episodes in the first third and fewer in the second third; and shorter latency to the first REM sleep episode and shorter NREM stage 2. Thus, their outcomes display that IDA is allied with long-lasting alterations in the temporal organization of sleep patterns. Peirano et al. [34] recommended that the changes in the neurotransmitter metabolism caused by iron deficiency, psychological status or a likely restless leg syndrome (RLS) influences sleep negatively. These outcomes might be clarified by some mechanisms. One possible explanation for the differences is that long-lasting effects of iron deficiency on the developing dopamine (DA) system are a promising example [35].

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 and IDA affects sleep quality irrespective of co-morbid psychiatric disorders such as depression and anxiety. And similarly, it was shown that subjective sleep quality was worse in patients with IDA when compared to non-anaemic patients.

REFERENCES

1. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated international restless legs syndrome study group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. (2014) 15:860–73.
2. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4(2):101-119.
3. "What Is Restless Legs Syndrome?". NHLBI. November 1, 2010. Archived from the original on 21 August 2016. Retrieved 19 August 2016.
4. "What Are the Signs and Symptoms of Restless Legs Syndrome?". NHLBI. November 1, 2010. Archived from the original on 27 August 2016. Retrieved 19 August 2016.
5. Patrick LR. Restless legs syndrome. Pathophysiology and the role of iron and folate. Altern Med Rev. 2007;12(2):101-112.
6. Picchietti DL, van den Eeden SK, Inoue Y, Berger K. Achievements, challenges, and future perspectives of epidemiologic research in restless legs syndrome (RLS). Sleep Med. (2017) 31:3–9.
7. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165(11):1286-1292.
8. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Mov Disord. 2011;26(1):114-120.
9. Winkelman JW. Considering the causes of RLS. Eur J Neurol. 2006;13(suppl 3):8-14.
10. Patton SM, Cho YW, Clardy TW, et al. Proteomic analysis of the cerebrospinal fluid of patients with restless legs syndrome/Willis-Ekbom disease. Fluids Barriers CNS. 2013;10(1):20.
11. Ferini-Strambi L. RLS-like symptoms: differential diagnosis by history and clinical assessment. Sleep Med. 2007;8(suppl 2):S3-S6.
12. Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med. 2007;357(7):639-647.
13. Allen RP, Earley CJ. The role of iron in restless legs syndrome. Mov Disord. 2007;22(suppl 18):S440-S448.
14. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994;23(3):200–203.
15. Ulfberg J, Nystr¨om 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(6):1159–1163.
16. O'Keeffe ST. Restless legs syndrome: a review. Arch Intern Med. 1996;156(3): 243–248.
17. Allen RP. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med. 2004;5(4):385–391.
18. Earley CJ, Connor J, Garcia-Borreguero D, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom disease). Sleep Med. 2014;15(11):1288–1301.
19. Daubian-Nose P, Frank MK, Esteves AM. Sleep disorders: a review of the interface between restless legs syndrome and iron metabolism. Sleep Sci 2014;7(4):234-7.
20. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. Sleep Med 2011;12:610-3.
21. Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol 2013;88(4):261-4.
22. Alsafadi S, Abaalkhail B, Wali SO, Aljammali K, Alotaiby B, Zakaria I, et al. Risk factors of primary and secondary restless legs syndrome among a middle-aged population in Saudi Arabia: A community-based study. Ann Thorac Med 2018;13:175-81.
23. Bae H, Kim KT, Heo MH, Do Y-R, Cho YW (2021) The prevalence and clinical characteristics of restless legs syndrome in patients with iron deficiency anemia in Korea. J Clin Sleep Med 17:1447–1452.
24. Connor JR (2008) Pathophysiology of restless legs syndrome: evidence for iron involvement. Curr Neurol Neurosci Rep 8:162–166.
25. Trenkwalder C, Allen R, Hogl B, Clemens S, Patton S, Schormair B et al (2018) Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol 17:994–1005.
26. Picchietti, M.A.; Picchietti, D.L. Advances in pediatric restless legs syndrome: Iron, genetics, diagnosis and treatment. Sleep Med. 2010, 11, 643–651.
27. Allen, R.P.; Picchietti, D.L.; Auerbach, M.; Cho, Y.W.; Connor, J.R.; Earley, C.J.; Garcia-Borreguero, D.; Kotagal, S.; Manconi, M.; Ondo,W. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: An IRLSSG task force report. Sleep Med. 2018, 41, 27–44.
28. Rosen, G.M.; Morrissette, S.; Larson, A.; Stading, P.; Barnes, T.L. Does improvement of low serum ferritin improve symptoms of restless legs syndrome in a cohort of pediatric patients? J. Clin. Sleep Med. 2019, 15, 1149–1154.
29. Hentze, M.W.; Muckenthaler, M.U.; Galy, B.; Camaschella, C. Two to tango: Regulation of Mammalian iron metabolism. Cell 2010, 142, 24–38.
30. Beard J(2003): Iron deficiency alters brain development and functioning. J Nutr., 133:468–472.
31. Kim J, Wessling-Resnick M(2014): Iron and mechanisms of emotional behavior. J Nutr Biochem.,25:1101–1107.
32. Dzirasa K, Ribeiro S, Costa S, Santos LM, Lin S-C, Grosmark A et al.(2006): Dopaminergic control of sleep- wake status. J Neurosci.,26:10577–10589.
33. Holst SC, Bersagliere A, Bachmann V, Berger W, Achermann P, Landolt HP(2014): Dopaminergic role in regulating neurophysiological markers of sleep homeostasis in humans. J Neurosci.,34:566–573.
34. Peirano PD, Algarín CR, Garrido MI, Lozoff B(2007): Iron deficiency anemia in infancy is associated with altered temporal organization of sleep states in childhood. Pediatr Res.,62:715–719.
35. Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR et al.(2006): Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. Behav Brain Res., 171:261–270.