

Association of hypo ferritinemia and restless legs syndrome in patients with iron deficiency anemia

M. Abbasi,¹ B. Safarzadehkhoushabi^{1*} and M S. Rabiei²

¹Department of Hematology, Hamadan University of Medical Sciences, Hamadan, Iran

²Department of Community Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

Restless legs syndrome (RLS) is one of the sleep disorders which affects sleep stages and causes repetitive awakenings. The patho physiology of RLS is not well defined, but there are some evidences about the role of iron deficiency in these patients. Therefore, in the current research we investigated the frequency of iron deficiency anemia in such cases. 143 patients referred to Hamedan University of Medical Sciences associated Hospital within the year 2015 with hypoferritinemia underwent a cross sectional study. All collected data were classified and analyzed by SPSS 16; t-test and chi-square tests. Of the 143 hypoferritinemic patients; 39 patients (27.3 %) met RLS criteria. Of that 17 cases (43.58 %) were male and 22 persons (56.41 %) were female. According to the study restless legs syndrome was significantly more common in women than men.(P-value = 0.01). Restless legs syndrome was significantly associated with serum ferritin levels in both sexes. And serum ferritin was significantly lower in men and women with non-infected people. (P-value <0.01). RLS was significantly more common in females than males. RLS was significantly higher in low ferritin levels. On the other hand its relation with low serum ferritin in both males and females is significant.

KEY WORDS: RESTLESS LEGS SYNDROME, HYPOFERRITINEMIA, IRON, ANEMIA

INTRODUCTION

Restless legs syndrome is a sleep disorder, including periodic limb movements in sleep (PLMS). A condition that occurs voluntary movements of limbs during sleep cycle and alters the level (stage) of sleep and waking are consecutive. Restless legs syndrome can be divided

into two types: type of family (primary) with known genetic component, and acquired (secondary). Primary type is seen in about fifty percent of first-degree relatives of patients and believed to have a hereditary defect in the metabolism of dopamine. Acquired type includes changes in the metabolism of iron in a range of patients, including pregnant women, and people with end stage

ARTICLE INFORMATION:

*Corresponding Author: Babak Safarzadehkhoushabi thesis.
irani@gmail.com

Received 29th Aug, 2016

Accepted after revision 30th Sep, 2016

BBRC Print ISSN: 0974-6455

Online ISSN: 2321-4007

 Thomson Reuters ISI ESC and Crossref Indexed Journal
NAAS Journal Score 2015: 3.48 Cosmos IF : 4.006

© A Society of Science and Nature Publication, 2016. All rights reserved.

Online Contents Available at: <http://www.bbrc.in/>

renal disease patients with iron deficiency and patients with Vitamin B12 deficiency. Periodic limb movements in sleep, such as restless legs syndrome may also occur in a situation such as Parkinson, Narcolepsy and other diseases with impaired dopamine production. The negative impact on quality of life is equal to or greater than chronic obstructive pulmonary disease or myocardial infarction. Severe restless legs syndrome causes the highest levels of sleep deprivation, among all sleep disorders after mania, (Trenkwalder, 1996, Montplaisir 2000, Allen, 2001 Mehmod et al., 2014 and Minár et al 2015).

The prevalence of PLMS is higher in the elderly. Maximally thirty percent of people over fifty years' experience the disease secondary to an underlying medical condition or drug side effects Restless legs syndrome is more common among elderly people and about ten to twenty percent of people over sixty-five years' experience the symptoms more specifically. The prevalence of the disease in women is doubled, (Ohayon, 2000, Rothdach, 2000 Allen, 2003). Studies in North America and northern Europe also confirm that the prevalence of restless legs syndrome (between five to twenty-five percent of the population) is common disease, (Zucconi, 2004).

The population whom are at risk for restless legs syndrome include: pregnant women, patients with end-stage renal disease, patients with a positive family history, patients with iron deficiency anemia, frequent blood donors, patients undergoing stomach surgery and children with hyperactivity syndrome- decreased attention and vitamin B12 deficiency. It seems characteristic feature of restless legs syndrome, is associated with circadian functional elements dopamine pathway. The circadian pattern of blood iron level is such that on the night, fifty to sixty percent below the level of serum iron in comparison to day. Patients prone to iron deficiency, have a greater chance of developing restless legs syndrome. These groups included patients undergoing gastric bypass surgery continuous blood donors as well as elderly, (Banerji, 1970, Tarquini, 1978, O'Keeffer, 1994, Hagan 1999, Silber, 2003, Borreguero, 2004, Earley, 2005 and Gamaldo, 2006 and Çurgunlu et al., 2012).

Restless Legs Syndrome also includes spontaneous or voluntary movement like walk, shrug, wrong handling or rubbing the legs on the bed for loss of sensation such as tingling, itching, burning, heave or electric shock is felt. Symptoms of this syndrome are the circadian pattern. So in the morning and evening worsen. About twenty percent of people with restless legs syndrome have no voluntary movements during sleep (therefore not required to identify). Although it causes severe sleep disturbance in most patients, and is known as one of the causes of sleep deficit in five to ten percent of Americans. Although restless legs syndrome is a common neurological motor disorder but under diagnosed and under

treated in many cases. On the other hand, due to lack of awareness of health staff about the syndrome, diagnosis and treatment of this syndrome is commonly missed, (Walters, 1995, Hening 2004 Wilson, 2005 and Curgunlu et al., 2012).

Researches on the prevalence of restless legs syndrome is not well established. The proper treatment of this syndrome needs recognizing the extent of it. Therefore it is concerned, Investigations about the prevalence of this syndrome, the age and sex of distribution in the society seems to be effective. The recognition of this disease by the medical staff will save the patients from ineffective treatments and sometimes misplaced and can take a step towards improving the quality of life in these patients.

MATERIAL AND METHODS

This study was cross sectional research which was conducted on patients with Hypoferritinemia, referring to Hamedan University of medical sciences associated Hospital in 2015. Inclusion criteria included: willingness to participate in the study, ferritin less than 50 mg per dL for women and less than 100 milligrams per deciliter for men.

Exclusion criteria included: impairment of consciousness (inability to respond to questions), physical-mental disability (inability to work with the researcher), drug addiction, current pregnancy (prone to anemia), sodium valproate or carbamazepine or gabapentin or hypnotic drugs (suppression of the symptoms of restless leg syndrome), Parkinson's disease (mimic symptoms of restless leg syndrome), history of renal failure (risk of anemia) and a history of gastric surgery (gastric bypass) (prone to anemia), diabetes mellitus (symptoms of neuropathy), history of diseases that can be seen in the process of neuropathy) malabsorption syndrome, a deficiency of vitamin B, Lyme disease, AIDS, cancer, malignancies of the blood system and reticuloendothelial).

Questionnaire Form which was used in this study, consisted of two parts. The first part included demographic information, including age, sex and place of residence (urban/rural), respectively. The second part of the questionnaire included five questions, the patient was asked by the researcher. All of these questions had yes or no answer and if first 4 questions answered (Yes) the diagnosis of restless legs syndrome was made for the individual. The last question was about the family history of the disease in her/his family. Some of the patients participating in the study refused. The numbers of patients providing inaccurate information were prevented from doing the proper research. To solve this problem, researchers questioned more patients to achieve the desired volume. The reliability and accuracy

was assessed during questioning meaning that patients with or without the necessary accuracy in speech, not included in this study.

Values were presented as Mean \pm Standard deviation (SD). For statistical analysis, SPSS software (Version 16, Chicago, IL, USA) was used applying chi 2 and T test. P < 0.05 was defined as significant. The study population voluntarily participated in the investigation. Verbal consent was obtained from the participants for publication of the research results.

RESULTS AND DISCUSSION

In this study, 143 patients referred to the clinic of Hamedan hospital in 2015 that do not qualify for exclusion criteria and met the inclusion criteria for the study were involved. Of these, 102 (71.3%) women and 41 (28.7%) were male. (Table 1,2,3,4)

The average age of women participating in the study was 34.35 ± 9.9 years and mean age was 45.8 ± 9.0 for men. Based on the findings of a CBC among the participants, 12 patients (8.4%) had iron deficiency anemia and 131 (91.6%) did not have iron deficiency anemia. The mean serum ferritin for women participated in the

Table 1: The distribution of cases in this series

Male	percent	female	percent	total
17	43.6	22	56.4	39(100%)
Low ferritin with iron deficiency anemia		Low ferritin without iron deficiency anemia		
5	12.8	34	87.2	39(100%)

Table 2: Frequency of restless legs syndrome in females based on ferritin levels

Serum ferritin level	Total females	restless legs syndrome cases
0-15	0	0
15-30	22	22
30-50	80	0

Table 3: Frequency of restless legs syndrome in males based on ferritin levels

Serum ferritin level	Total males	restless legs syndrome cases
0-15	1	0
15-30	29	7
30-50	11	10

Table 4: Frequency of restless legs syndrome in females based on age groups		
Serum ferritin level	Total females	restless legs syndrome cases
0-30	42	0
30-50	50	18
More than 50	10	4

Table 5: Frequency of restless legs syndrome in males based on age groups		
Serum ferritin level	Total males	restless legs syndrome cases
0-30	0	0
30-50	0	0
More than 50	41	17

project was 35.87 ± 9.4 mg per deciliter and for men was 64.0 ± 21.0 mg per deciliter.

According to the study, 39 cases (27.3%) of patients with low ferritin diagnosed with restless legs syndrome And 104 (72.7%) cases did not express symptoms of this syndrome. The mean serum ferritin level in patients was 29.33 ± 9.9 mg per deciliter versus 49.43 ± 18.34 mg per dL in healthy cases. The average age of men suffering from this syndrome was 54 ± 6.12 years and in females was 45.045 ± 5.5 . Serum Ferritin level was 40.11 ± 2.2 mg per deciliter in men with this syndrome and this amount was 21 ± 2.5 for women. Moreover, 7 cases (17.9%) of the patients had a positive family history for this syndrome. And 32 (82.1%) had no family history. In contrast, 104 (72.72%) of patients with low ferritin levels were not affected by restless legs syndrome. Of these, 80 patients (76.92%) were women and 24 (23.07%) were male, (Table 2,3,4).

According to the study restless legs syndrome was significantly more common in women than men. (P-value = 0.01). In this study, it was confirmed that restless legs syndrome is not associated with iron deficiency anemia significantly. (P-value = 0.24). According to the study restless legs syndrome was significantly associated with serum ferritin levels in both sexes. And serum ferritin was significantly lower in men and women with non-infected people. (P-value <0.01) Ferritin levels in women with this syndrome was associated, significantly (P-value <0.01), but the men were not able to determine the significance of the data. In this study, positive family history of the syndrome did not approved. (P-value = 0.75) Restless legs syndrome in both sexes were also significantly associated with age and was more common in older age. (P-value <0.01).

According to the findings of our research it was found that restless legs syndrome was significantly seen in lower levels of ferritin. The syndrome is more common in women but not significantly correlated with anemia. Çurgunlu and colleagues in Turkey in 2012 reported that the restless legs syndrome in patients with low ferritin level was more frequent, (Çurgunlu et al., 2012).

Restless legs Syndrome (RLS) is a kind of sleep disorders; disturbing sleep stages and causes repetitive awakens. High risk populations for RLS including: pregnant ladies, end stage renal disease patients, patients with familial history for that, patients with iron deficiency anemia, chronic blood donors and patients with gastric bypass surgery and kids with ADHD and people with vitamin B12 deficiency. The diagnosis of RLS consists of four essential clinical criteria based solely on symptoms: A sensation of an urge to move the limbs (commonly legs); is usually associated with paresthesia. Onset or worsening of symptoms when at rest; are not associated with any specific body position. Relief of symptoms with movement; complete relief immediately or shortly after initiating movement was also seen. Marked circadian variation in degree or occurrence of symptoms; worse in the evening, got improved in the morning, regardless of quality or quantity of sleep.

Although Hogl and colleagues in 2005, did not reveal any relationship between levels of serum ferritin; and transferrin levels in serum, levels of free iron and restless legs syndrome, however, stated that the soluble transferrin receptor (sTR) was significantly lower in patients with this syndrome. In this study, high levels of serum sTR was independent predictor of the risk of restless legs syndrome, (Hogl, 2005).

This study, like those of Rothdach *et al* (2000), Ohayon *et al* (2002) and Zucconi *et al* (2004), presently reports that the syndrome is more common in older ages, which is similar to the above findings. Bjorvatn and colleagues in a study in 2005 have also found that the age wise prevalence of this syndrome existed in two Scandinavian countries, being in cases of older than 30 years, on the other hand, there were no significant relationships with age as reported by Bjorvatn *et al.*, (2005).

In this study, 17.9% of the participants had a positive family history for this syndrome. Although this percentage is about 40-60% which was reported by Zucconi *et al*, (2004) but a significant relationship was not found in our study. That's probably due to lack of recognition of this syndrome in the past by the public and health professionals (Zucconi 2004). Çurgunlu et al., have stated that the prevalence of this syndrome in women is two times more than men. This finding has also been confirmed by Ohayon (2002) and Zucconi, (2004). In our study, the relationship between restless legs syndrome and serum ferritin was observed. Although more

studies are needed to confirm or refuse this theory. In a study conducted by Blake *et al.* (1976), it has been reported that iron is required for the production of tyrosine hydroxylase which is the limiting step in the production. Some recent workers have reported that patients who had serious symptoms of restless leg syndrome, got it declined by supplements of iron, (Connor, *et al.*, 2003, Mehmood *et al.*, 2014 and Minár *et al* 2015). Likewise, we also report in this paper that serum iron level disturbances play a significant role in the pathophysiology of restless legs syndrome.

CONCLUSION

Finally, this study concluded that the frequency of restless legs syndrome in patients with low ferritin is about 27.3%. This syndrome was significantly associated with reduced levels of serum ferritin. Also this syndrome in elderly and especially in women is more prevalent. Further studies with larger sample size and prospective in urban and rural centers, specialized treatment centers needs to be done. It is suggested based on the findings of this study, subjects with low serum ferritin, even without laboratory findings of anemia, to improve the quality of sleep, or prevent the syndrome can be treated with oral iron supplements.

REFERENCES

- Allen RP, Earley CJ.(2001) Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol*;18:128-147.
- Allen RP, Picchietti D, Hening WA.(2003) 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*;4:101-119.
- Banerji N, Hurwitz LJ. (1970) Restless legs syndrome, with particular reference to its occurrence after gastric surgery. *Br Med J*;4:774-775.
- Blake DR, Williams AC, Pall H.(1986) Iron and akathisia. *Br Med J*;292:1393.
- Bjorvatn B, Leissner L, Ulfberg J. (2005) Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. *Sleep Med*;6:307-312.
- Connor JR, Boyer PJ, Menzies SL.(2003) Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology*;61:304-309.
- Çurgunlu A, Döventas A, Karadeniz D, Erdinçler DS, Oztürk AK, Karter Y, Yaldıran A, Sipahioglu F, Beger T.(2012) Prevalence and characteristics of restless legs syndrome (RLS) in the elderly and the relation of serum ferritin levels with disease severity: hospital-based study from Istanbul, Turkey. *Arch Gerontol Geriatr*; 55:73-76.

- Earley CJ, Connor JR, Beard JL.(2005) Ferritin levels in the cerebrospinal fluid and restless legs syndrome: effects of different clinical phenotypes. *Sleep*;28:1069-1075.
- Gamaldo CE, Earley CJ.(2006) Restless legs syndrome: a clinical update. *Chest*;130:1596-1604.
- Garcia-Borreguero D, Serrano C, Larrosa O, Granizo JJ.(2004) Circadian effects of dopaminergic treatment in restless legs syndrome. *Sleep Med*;5:413-420.
- Hagan MM, Havel PJ, Seeley RJ.(1999) Cerebrospinal fluid and plasma leptin measurements: covariability with dopamine and cortisol in fasting humans. *J Clin Endocrinol Metab*;84:3579-3585.
- Hening W, Walter AS, Allen RP. (2004) Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med*;5:237-246.
- Hogl B, Kiechl S, Willeit J. (2005) Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. *Neurology*;64:1920-1924.
- Mehmood T, Auerbach M, Earley CJ, Allen RP.(2014) Response to intravenous iron in patients with iron deficiency anemia (IDA) and restless leg syndrome (Willis-Ekbom disease). *Sleep Med*;15(12):1473-6. doi: 10.1016/j.sleep.2014.08.012.
- Minár M, Košutzká Z, Habánová H, Rusnák I, Planck K, Valkovic P.(2015) Restless legs syndrome in pregnancy is connected with iron deficiency. *Sleep Med*;16(5):589-92. doi: 10.1016
- Montplaisir J, Michaud M, Denesle R, Gosselin A.(2000) Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. *Sleep Med*;1:163-167.
- Ohayon MM, Roth T. (2000) Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res*;53:547-554.
- O'Keeffe ST, Gavin K, Lavan JN.(1994) Iron status and the restless legs syndrome in the elderly. *Age Ageing*;23:200-203.
- Rothdach AJ, Trenkwalder C, Haberstock J.(2000) Prevalence and risk factors of RLS in an elderly population: the MEMO study. *Memory and Morbidity in Augsburg Elderly*. *Neurology*;54:1064-1068.
- Silber MH, Richardson JW.(2003) Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. *Mayo Clin Proc*;78:52-54.
- Tarquini B.(1978) Iron metabolism: clinical chronobiological aspects. *Chronobiologia*;5:315-336.
- Trenkwalder C, Seidel VC, Gasser T, Oertel WH.(1996) Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. *Mov Disord*;11:389-394.
- Walters AS.(1995) Toward a better definition of restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord*;10:634-642.
- Wilson JF. (2005) Is sleep the new vital sign? *Ann Intern Med*;142:877-880.
- Zucconi M, Ferini-Strambi L.(2004) Epidemiology and clinical findings of restless legs syndrome. *Sleep Med*;5:293-299.