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Review Article

# Sleep disorders: A review of the interface between restless legs syndrome and iron metabolism

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ABSTRACT

Restless legs syndrome (RLS) is characterized by unpleasant sensations mainly in the legs. 43% of RLS-associated conditions have also been associated with systemic iron deficiency. The objective of this study was to review in the literature the relationship between iron metabolism and RLS. With an initial search using the keywords combination "Iron Metabolism OR Iron Deficiency AND Restless Legs Syndrome," 145 articles were screened, and 20 articles were selected. Few studies were found for this review in the period of 2001–2014, however, the correlation between RLS and iron was evident.



## 1. Introduction

Restless legs syndrome (RLS) is characterized by uncomfortable sensations in the lower limbs, although other body parts such as the arms may be affected [1,2]. The symptoms are described as sensations such as 'creeping,' 'crawling,' 'tingling,' 'burning,' 'cramping,' 'itching,' 'electric chocks,' 'stinging,' 'tension' or 'discomfort' in the lower limbs between the ankle and the knee [3].

There are two types of RLS: idiopathic and symptomatic (secondary) [4]. The pathophysiology of idiopathic and secondary RLS is incompletely understood, local reduction of dopamine content/expression in the central nervous system seems to be a major cause of the symptoms [1,2].

Since the etiology of RLS is unknown, a central organizing concept is needed to explain the vast number of conditions that trigger this well-defined syndrome, reasonable therapeutic improvement by various pharmacological agents, the evolving role of iron regulation and the various genetic loci that have been associated with RLS in selected populations. Reliable studies have demonstrated that 50% of restless legs syndrome patients have a positive family history and it has been suggested that RLS is a highly hereditary trait [4,5]. Restless legs syndrome is one of the few common neurological disorders that exhibits significant familial aggregation [6]. Oexle et al. [7] found a correlation between RLS and iron parameters in serum, but, it may be weaker than assumed.

In Weinstock and Walters [8], 43% of RLS-associated conditions have also been associated with systemic iron deficiency. Iron is distributed heterogeneously in different regions and brain cells; brain iron homeostasis is required for

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its normal function [9]. Iron deficiency is undoubtedly the most common nutritional disorder worldwide, affecting more than 2 billion people ([10] apud [11]). Iron has a fundamental function on the correct dopaminergic system operation, particularly being a coenzyme of Tyrosine Hydroxylase; the evidences that show us a possible dopaminergic dysfunction are several; most of the genes involved have a relationship with dopamine metabolism (gene of receptor D2, gene of receptor D4 DRD4, gene of dopamine transporter DAT 1), and the recent articles of functional neuroimaging bring a dopaminergic dysfunction at the level of frontoestriatal circuit [12].

Thus, the objective of this study is to review in the literature the relationship between the influences of iron metabolism in RLS.

## 2. Methods

A search on PubMed was established and the keywords used in this search were 'Iron Metabolism,' 'Iron Deficiency' and 'Restless Legs Syndrome'; 145 articles were screened and we divided them into different topics (Table 1). Discussions occurred to select the articles within the stipulated period 2001 and 05/08/2014 and the chosen keywords, and, 20 articles of the 145 found were selected. The following data were extracted: (1) study design, (2) patients characteristics, such as number of volunteers, age and gender and (3) consequences of iron deficiency in RLS. Articles between 2001 and 05/08/2014 were used in the study. As inclusion criteria, we used references that reflect our personal selection of articles as being the most informative, using only English articles.

## 3. Results

### 3.1. *Studies of the influences of iron metabolism in RLS*

#### 3.1.1. *Relation with attention deficit hyperactivity disorder (ADHD)*

Oner et al. [4] found RLS in 29 (33%) of the 87 ADHD children and adolescent participants, they showed that depleted iron stores might increase the risk of having RLS in ADHD subjects, suggesting a correlation between RLS and ADHD. On the other hand, Soto-Insuga et al. [12] did a study with 60 participants (mean 9,02 years), and found patients with iron deficiency and SPI, but did not reach any result of statistical significance.

**Table 1 – Topics of the 145 articles screened.**

| Topics | Number of articles |
|---|---|
| Restless legs syndrome | 38 |
| Atention deficit hyperactivity disorder | 5 |
| Dopaminergic system disturbance | 18 |
| Pregnancy | 5 |
| Iron metabolism | 33 |
| Supplementation | 9 |
| Iron genes | 10 |
| Pharmacological treatment | 23 |
| Periodic limb movement | 4 |

#### 3.1.2. *Dopaminergic system disturbance (DSD)*

Several markers are important to know about dopaminergic system, we included the dopamine, DAT (dopamine transporter), dopamine receptors (DR1, DR2, DR3), Tyrosine hydroxylase (TH), found in putamen and substantia nigra.

Iron deficiency can be indicative of reduced activity of the dopamine transporter (DAT) [11]. Earley et al. [13] found a significant decrease in DAT in two independent studies; these results when viewed along with prior RLS, SPECT and autopsy studies of DAT, and cell culture studies with iron deficiency and DAT, suggest that membrane-bound striatal DAT, but not total cellular DAT, may be decreased in RLS.

It is likely that majority of RLS patients have no degeneration of dopaminergic neurons, which means that the machinery to synthesize dopamine is not impaired [1].

In another point of view Connor et al. [14], in RLS tissue, compared with controls, a significant decrease in D2R in the putamen that correlated with severity of the RLS; RLS also showed significant increases in TH in the substantia nigra, compared with the controls, but not in the putamen. Both TH and phosphorylated (active) TH were significantly increased in the substantia nigra and putamen; there were no significant differences in either the putamen or nigra for D1R. These results support the idea that disturbance on dopaminergic system can be the mean factor to symptoms of RLS. Results confirm the ability of iron deficiency and D3R−/− to evoke sensory and motor symptoms in mice resembling those observed in the RLS patients [15].

#### 3.1.3. *Pregnancy*

Prevalence and characteristics of RLS is more common in women than in men [16]. RLS is much more common in pregnant (approximately 26%) than in non-pregnant women and frequently becomes worse or may appear for the first time during pregnancy [17]. Lower hemoglobin levels and supplementation deficits of iron and vitamins in pregnant women can indicate a possible risk factor for RLS in pregnancy [18]. A few weeks after therapy, both patients experienced a significant reduction or even remission of RLS symptoms; their quality of life and sleep substantially improved and no treatment-related adverse effects were observed [19].

#### 3.1.4. *Iron deficiency anemia (IDA)*

Ferritin is increased in a number of conditions unrelated to iron status. This may cause a false normal value in an individual with truly low iron stores. Thus, a low value of ferritin is indicative of true iron deficiency [20]. Allen et al. [21] evaluated 251 patients, and they found for the first time a reasonably accurate estimate of RLS prevalence in a community population of patients with IDA referred for treatment, thus confirming the expectation of high prevalence of clinically significant RLS in IDA.

#### 3.1.5. *Supplementation*

We can still have a discussion on literature about the oral iron and intravenous iron sucrose. Mohri et al. [22] did a study with 30 Japanese children with RLS, and the treatment with oral iron supplementation was reported to be highly effective in 17 children, effective in 10, and ineffective in 3 as Grote et al. [2] found RLS scores consistently lower after using intravenous iron sucrose, compared with placebo during all

the treatment. According to Birgegård et al. [23], intravenous iron sucrose substitutes iron loss in blood donors more efficiently compared with oral iron sulfate, especially in women.

#### 3.1.6. *Iron genes*

Several lines of evidence suggest a hereditary link in patients with idiopathic RLS; genetic linkage studies of large families with many members affected by RLS have identified many candidates' susceptibility [24]. Five gene variants have been linked to RLS [25]. The functions of the five genes that were identified (MEIS1, BTBD9, MAP2K5, LBXCOR1 and PTPRD) [26], in addition, the gene BTBD9 in humans, have been associated with restless legs syndrome and serum ferritin [27].

## 4. Conclusion

The pathophysiology of RLS remains unclear, although roles for dopamine dysfunction and brain iron deficiency have been proposed [28]. A low ferritin level (< 50 ng/ml) is documented in the literature to be related to RLS in the general population [29]. Dysregulation of iron metabolic pathways has been demonstrated in a large number of neurodegenerative movement disorders [30]. Serum iron levels have relationships with sleep quality, daytime sleepiness, depression, fatigue, and quality of life [31].

Literature suggests future studies relating to levels of iron and pregnancy, ADHD and RLS. Measurement of hepcidin or pro-hepcidin in all RLS-associated disorders and determination of whether reduction of inflammation by treating the underlying systemic disorder could improve RLS symptoms and alter CNS and/or peripheral hepcidin and iron level also are important. And another point is exploring immunological and inflammatory properties of NOS, nitric oxide and the hypoxia inducible in the pathway of RLS [5].

There are a lot of consensuses and evidences about RLS, but the study and advances in research bring a line to investigate the syndrome. Articles show the syndrome in children, adolescents, adults and in pregnant women (in different populations around the world), but the study's line has been moving to iron deficiency. Few studies were found (145) for this review in the period of 2001–2014, however, the correlation between RLS and iron was evident as shown in the articles about ADHD, dopamine system disturbance, pregnancy, IDA, supplementation and iron genes.

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## REFERENCES

[1] García-Borreguero D, Williams AM. Dopaminergic argumentation of restless legs syndrome. Sleep Med Rev 2010;14:339–46.
[2] Grote L, Leissner L, Hedner J, Usfberg 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;24:1445–52.
[3] Spolador T, Allis JC, Pondé MP. Treatment of restless legs syndrome. Revista Brasileira de Psiquiatria 2006;28:308–15.
[4] Oner P, Dirik EB, Taner Y, Caykoylu A, Anlar O. Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. Tohoku J Exp Med 2007;213:269–76.
[5] Weinstock LB, Walters AS, Paueksakon P. Restless legs syndrome – Theoretical roles of inflammatory and immune mechanisms. Sleep Med Rev 2012;16:341–54.
[6] Xiong L, Montplaisir J, Desautels A, Barhdadi A, Turecki G, Levchenko A, Thibodeau P, Dubé M, Gaspar C, Rouleau GA. Family study of restless legs syndrome in Quebec, Canada. Arch Neurol 2010;67:617–22.
[7] Oexle K, Schormair B, Ried JS, Czamara D, Heim K, Frauscher B, Högl B, Trenkwalder C, Fiedler MG, Thiery J, Lichtner P, Prokisch H, Specht M, Müller-Myhsok B, Döring A, Gieger C, Peters A, Wichmann H-E, Meitinger T, Wilkelmann J. Dilution of candidates: the case of iron-related genes in restless legs syndrome. Eur J Hum Genet 2013;21:410–4.
[8] Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. Sleep Med 2011;12:610–3.
[9] Menegassi M, Mello ED, Guimarães LR, Matte BC, Driemeier F, Pedroso GL, Rohde LA, Schmitz M. Food intake and serum levels of iron in children and adolescents with attention-deficit/hyperactivity disorder. Revista Brasileira de Psiquiatria 2010;32:132–8.
[10] World Health Organization. Iron Deficiency Anemia – Prevention and Control. A guide for programme managers; 2001.
[11] Bianco LE, Wiesinger J, Earley CJ, Jones BC, Beard JL. Iron deficiency alters dopamine uptake and response to L-DOPA injection in Sprague-Dawley rats. J Neurochem 2008;106:205–15.
[12] Soto-Insuga V, Calleja ML, Prados M, Castaño C, Losada R, Ruiz-Falcó ML. Utilidad del hierro em el tratamiento del trastorno por déficit de atención e hiperactividad. Anales de Pediatría 2013;79:230–5.
[13] Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas R, Brasic J, Ravert HT, Dannals RF, Allen RP. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. SLEEP 2011;34:341–7.
[14] Connor JR, Wang X, Allen RP, Beard JL, Wiesinger A, Felt BT, Earley CJ. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain 2009;132:2403–12.
[15] Dowling P, Klinker F, Stadelmenn C, Hasan K, Paulus W, Liebetanz D. Dopamine $D_3$ receptor specifically modulates motor and sensory symptoms in iron-deficient mice. J Neurosci 2011;31:70–7.
[16] Çurgunlu A, Döventaą A, Karadeniz D, Erdinçler DS, Öztürk AK, Karter Y, Yaldıran A, Sipahioğlu F, Beğer T. 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 2012;55:73–6.
[17] Pereira JRJC, Silva IRR, Pradella-Hallinan M. Transient Willis–Ekbom's disease (restless legs syndrome) during pregnancy may be caused by estradiol-mediated dopamine overmodulation. Med Hypotheses 2013;80:205–8.

[18] Tunç T, Karadağ YS, Doğulu F, İnan LE. Predisposing factors of restless legs syndrome in pregnancy. Mov Disord 2007;22:627–31.
[19] Vadasz D, Ries V, Oertel WH. Intravenous iron sucrose for restless leg syndrome in pregnant women with low serum ferritin. Sleep Med 2013;14:1214–6.
[20] Mackie S, Winkelman JW. Normal ferritin in a patient with iron deficiency and rls. J Clin Sleep Med 2013;9:511–3.
[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;88:261–4.
[22] Mohri I, Kato-Nishimura K, Kagitani-Shimono K, Kimura-Ohba S, Ozono K, Tachibana N, Taniike M. Evaluation of oral iron treatment in pediatric restless legs syndrome (rls). Sleep Med 2012;13:429–32.
[23] Birgegård G, Scneider K, Ulfberg J. High incidence of iron depletion and restless leg syndrome (RLS) in regular blood donors: intravenous iron sucrose substitution more effective than oral iron. Int J Transfus Med 2010;99:354–61.
[24] Winkelman JW. Considering the causes of RLS. Eur J Neurol 2006;13:8–14.
[25] Picchietti MA, Picchietti DL. Advances in pediatric restless legs syndrome: iron, genetics, diagnosis and treatment. Sleep Med 2010;11:643–51.
[26] Trenkwalder C, Paulus W. Restless legs syndrome: pathopysiology, clinical presentation and management. Nat Rev Neurol 2010;6:337–46.
[27] Jellen LC, Beard JL, Jones BC. Systems genetics analysis of iron regulation in the brain. Biochimie 2009;91:1255–9.
[28] Thorpe AJ, Clair A, Hochman S, Clemens S. Possible sites of therapeutic action in restless legs syndrome: Focus on dopamine and $\alpha_2\delta$ ligands. Eur Neurol 2011;66:18–29.
[29] Lee KA, Zaffke ME, Baratte-Beebe K. Rest legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Women's Health Gender-Based Med 2001;10:335–41.
[30] Dusek P, Jankovic J, Le W. Iron dysregulation in movement disorders. Neurobiol Dis 2012;46:1–18.
[31] Cuellar NG, Hanlon A, Ratcliffe SJ. The Relationship whit iron and health outcomes in persons with restless legs syndrome. Clin Nurs Res 2011;20:144–61.