Review article

Restless Legs Syndrome and Iron

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Abstract

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is one of the most common neurological disorders that significantly affects quality of life and sleep. It manifests itself in involuntary movements of the lower limbs due to the feeling of discomfort and restlessness that patients feel in their lower limbs.

RLS is of great interest to the experts in various fields of medicine, especially to neurologists, general practitioners, internists and psychiatrists. Numerous clinical conditions and diseases play a role in the pathophysiology of RLS. Some of them are pregnancy, some kidney and stomach diseases, iron deficiency and some disorders of the metabolism.

Moreover, iron is a very important micronutrient in the human body. It is involved in many metabolic processes and, in addition to RLS, it is also associated with other diseases such as hemochromatosis and anemia. This neurological disorder has wide therapeutic choices, which include lifestyle changes, dopaminergic agonists, opioids and iron therapy. Many non-anemic patients with RLS showed reduced levels in brain iron levels compared to healthy control groups in several research. The best course of treatment for this group of patients is iron supplementation.

Oral iron supplementations are the first choice of therapy for patients with low serum ferritin levels. However, when serum ferritin levels are normal or high or when oral iron is not tolerated, intravenous iron is a better choice. There are many intravenous iron formulations, but low molecular weight dextran and ferric carboxymaltose have very efficient effects on the treatment of RLS.

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Introduction

Restless legs syndrome (RLS) has been described as a neurological disorder, related to uncontrolled leg movements, and, in much smaller number of patients, it is associated with uncontrolled hand movements. Uncontrolled limb movements are preceded by a sense of discomfort, described by patients as annealing, burning, tickling, etc. It occurs more frequently

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during inaction. Therefore, it is a common cause of sleep disorders (1-3). In the 17th century, sir Thomas Willis noticed the connection between sleep disorders and lower extremity discomfort among his patients. However, Karl- Axel Ekbom first used the term 'restless legs syndrome' in 1945. That is why this disorder is also known as Willis-Ekbom disease (4).

Unlike some other disorders with similar problems, such as polyneuropathy, the symptoms of RLS decrease with leg movements. In most cases, it is a chronic disorder with worsening symptoms, which vary in intensity and frequency. Therefore, in patients with chronic form of this disorder, symptoms occur at least twice a week if patients do not follow their therapy (1, 5).

RLS has prevalence between 8 and 10% (6) in adult and 2% in children population (7). The study conducted by Manconi et al. has shown that RLS occurs more frequently in women, age 35 and above, than in men of the same age (8).

This disorder can be inherited or be a result of a clinical condition such as kidney diseases (hemodialysis patients) (9), pregnancy (evaluated progesterone and estrogen levels, iron deficiency) (10), anemia, stomach damage, etc. In addition, some substances such as neuroleptic drugs, caffeine, lithium, metoclopramide, antihistamines, dopaminergic agents (1, 11) may increase the risk of developing RLS symptoms (Figure 1).

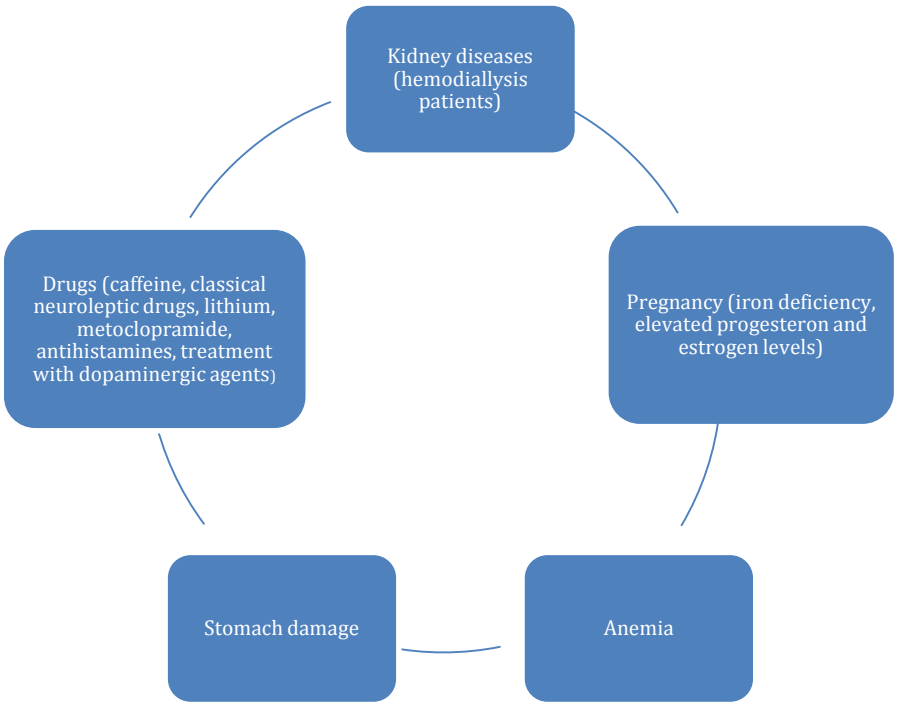

Figure 1. Non-hereditary causes of restless legs syndrome

Summarized findings from studies to date on the most common diseases/clinical conditions/drugs that are associated with restless legs syndrome.

Treatment for RLS depends on its cause. Therefore, the treatment can include dopaminergic agents, lifestyle changes, iron therapy, α-2-δ- ligands, opioids, etc (1). Compared to the previous European Federation of Neurological Societies (EFNS) guidelines on the management of RLS from 2004, new guidelines from 2012 bring news. Numerous drug studies have been made during this period and new treatments have been examined that could be a potential therapy for RLS. The majority of research deals with dopaminergic

agents, considered the first line therapy. The crucial role of iron in pathophysiology of RLS has also been confirmed. Alternative forms of therapy have been investigated; folate, vitamin E, physiotherapy, aerobic training and magnesium. Nevertheless, there is still not enough evidence of their effectiveness (12).

Iron in relation to health and diseases

Iron is one of the most important micronutrient in human body. It has many functions such as a role in metabolic processes; it can cause oxidative stress because it participates in the formation of oxygen radicals (13), and it is a cofactor of numerous enzymes (13, 14).

There are about 4,2 grams of iron in the human body, and much of it is bound to hemoglobin and involved in oxygen transfer (12). About 10% of the iron ingested through food is absorbed in the digestive system, mostly in the duodenum (15).

Ferritin is an intracellular protein that stores iron and plays an important role in regulating iron homeostasis, while transferrin is a glycoprotein that binds iron and transports it into the cells (16). The major regulator of iron homeostasis is hepcidin, 25-amino acid peptide hormone, which is mainly secreted by hepatocytes (17, 18). Its deregulation is linked with excess iron and iron deficiency. Therefore, when level of hepcidin is very high, like in case of inflammation, the absorption of iron is reduced and this can lead to the development of anemia (17-19).

It is proved that brain and liver contain high levels of iron (13). The highest concentration of brain iron is found in substantia nigra, globus pallidus, red nucleus, putamen and dentate nucleus of the cerebellum (20, 21). In oligodendrocytes, the presence of the transferrin has been confirmed, but a greater amount of brain iron is nevertheless related with ferritin (13, 22). Iron plays a large role in neurotransmitter synthesis and mitochondrial respiration and its status is regulated at the level of the blood- brain barrier (BBB) (13, 23, 24).

It has long been known that iron excess causes hemochromatosis, characterized by skin changes, weakness, loss of sex drive, abdominal pain and symptoms of diabetes; but recent studies have associated brain iron excess with the onset of neurodegenerative diseases such as Parkinson's disease. On the other hand, iron deficiency in the central nervous system (CNS) is associated with irritability, concentration disorder, tiredness and it may play a role in the pathophysiology of RLS (13).

Correlation between restless legs syndrome and iron

The first person who noticed that low serum iron level could be a risk factor for developing restless legs syndrome was Nordlander (25, 26). Ekbom observed iron deficiency among his patients. Although he noticed repeated occurrence of low iron level in RLS, most of his patients suffered from uremia, anemia or were pregnant women (27). In another research, O'Keeffe found low serum iron and ferritin values in patients who complained of RLS symptoms. It was observed that the lower the ferritin level were, the more severe RLS symptoms appeared (28, 29). Iron supplementation has caused improvement in some patients. The potential cause of this is altered management of brain iron in patients with RLS (30, 31).

Two studies have shown that almost 2/5 of the patients suffering from iron deficiency anemia also had symptoms of RLS. Nevertheless, these studies used small groups of participants (32, 33). However, one study, conducted by Allen et al. among the general population, has shown that the percentage of people with symptoms of RLS is several times higher in the group of participants with iron deficiency anemia than in the general population (34). Abnormalities in the concentrations of ferritin, transferrin in the cerebrospinal fluid (CSF), low CSF ferritin, and high CSF transferrin levels have been noticed (35).

Circadian pattern is characteristic for RLS, with symptoms being dominant at nighttime. Serum iron has a circadian variation, with 30 to 50% drop at night. This can lead to clinically significant

drop in brain iron levels with patients with RLS and create the symptoms (36).
Lower iron concentration in substantia nigra and putamen were found in some patients with idiopathic RLS and capillary transport of iron in the brain probably plays a major role in this. In addition, it has been observed that the iron levels in substantia nigra increase with aging (37-39).
There is a small number of studies that have compared the connection between serum hepcidin levels and RLS. However, one of them found higher prohepcidin (inactive form of hepcidin) in putamen and substantia nigra in patients with RLS. This opens up the possibility of discovering new medications, such as hepcidin antagonists, for the treatment of RLS (40-42).

Iron treatment

Iron deficiency anemia is present in more than 1/5 of the patients with RLS (34). Accordingly, oral and intravenous iron supplements are used as therapy for those patients. When serum ferritin level is lower than 75 μg/l, oral iron supplementation is the therapy of choice. While in patients with serum ferritin level higher than 300 μg/l intravenous iron preparations are a better choice (43, 44). O'Keeffe observed among his patients, who had different serum ferritin values, that oral iron supplements had better effect on patients with lower serum ferritin values. However, the problem with this study was that it did not have a control group (25, 29). Furthermore, oral iron supplements have almost the same effect whether taken once a day or divided into two doses. In addition, in both cases these supplementations should be taken with vitamin C in order to improve absorption in the small intestine (44, 45).

According to the American Academy of Sleep Medicine (AASM) guidelines, iron treatment is effective for RLS only in patients who have low ferritin levels. In addition, it is preferred oral over parenteral iron formulations, because parenteral forms are associated with a number of side effects that can endanger patients' life and health (46).

On the other hand, intravenous iron supplementations bypass the intestinal- blood barrier and restriction of iron absorption (47). Intravenous iron forms take precedence over oral iron only in two cases. First is when the patient is severely bleeding and rapidly losing iron, and the second case is when patients have problems with oral iron absorption (44, 48).

There are several intravenous iron formulations available: ferric carboxymaltose, iron sucrose, iron gluconate, low and high molecular weight dextrans (LMW and HMW dextrans), ferumoxytol and iron isomaltose (44). LMW dextran and ferric carboxymaltose have the best clinical evidences for treatment of RLS (1, 44). Infusion of 1000 mg LMW dextran improves the health of RLS patients with early symptoms and significantly increases iron levels in substantia nigra (49). Both oral and intravenous iron preparations have numerous limitations in the treatment of RLS. The most dangerous side effect is related to HMW dextran and it involves anaphylactic shock. On the other hand, ferric carboxymaltose is safe to use because its side effects, such as nausea and headache, are much milder (50).

There are not enough studies on intravenous sucrose, as well as on most intravenous iron preparations. Nevertheless, it is known that intravenous sucrose is not effective for patients that do not have anemia (50). In addition, for iron gluconate, ferumoxytol and iron isomaltose, there are insufficient clinical evidences (44, 51) (Table 1)..

Table 1. Iron preparation limitations in the treatment of restless legs syndrome

Oral ferrous sulfate:	gastrointestinal upset; not effective for patients with serum ferritin level>75 µg/l
Ferric carboxymaltose:	headache nausea
Iron sucrose:	not effective in iron deficiency patients without anemia
High molecular weight dextran:	high incidence of anaphylactic shock
Low molecular weight dextran:	not so effective in patients with symptoms of late onset RLS
Iron isomaltose, ferumoxytol, iron gluconate:	not enough clinical evidences

Note: Summarized findings from studies to date on oral and intravenous iron preparations for the treatment of restless legs syndrome.

Avni et al. have proven in their research that iron preparations are safe and effective for RLS. However, there is still a great need for further research, especially for the research that could determine the exact drug dosages and therapeutic regimen (43)

Conclusion

Numerous studies on the relationship between RLS and iron in the body have provided better insight into the pathophysiology of this disorder and have opened up new possibilities related to therapeutic approaches, such as hepcidin antagonists. Nevertheless, there are still many uncertainties related to iron therapy and a need for further research on that topic. The reason is the fact that many intravenous iron formulations lack sufficient clinical evidences regarding their effect on reducing the symptoms of RLS. Furthermore, many studies have a small or inadequate sample of participants. In addition, for many intravenous iron formulations the exact dosage required for the treatment of RLS has not been determined..

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