Understanding the Relationship Between Iron and Restless Legs Syndrome

Brain Iron Plays a Role

Research conducted over the past two decades has deepened our understanding of the relationship between iron and restless legs syndrome (RLS). Scientists have found that brain iron deficiency plays a role in the development of RLS. Consensus-based clinical treatment guidelines, published in 2018, provide direction for appropriate clinical management of RLS.[1] These guidelines recommend iron treatment when serum ferritin, the primary storage unit for iron, is found to be in the low normal range (≤ 100 mcg/L). Serum ferritin is a peripheral measure of iron that has been found to correlate inversely with RLS symptom severity.[2,3] When serum ferritin level is low, it is postulated that iron levels in the brain will also be low and this may cause or worsen RLS symptoms.

The Role of Iron in the Body

Iron is essential to all living cells in the body. Different proteins regulate the distribution of iron throughout the body. Transferrin is responsible for transporting iron to the different organs whereas ferritin, in large part, is responsible for storage of iron within each cell.

When dietary or supplemental iron enters the bloodstream, about 80-85% will go to bone marrow, where it will be used to make red blood cells. The next largest proportion of iron is distributed to the liver. A small percentage – less than 5% – is distributed to other organs, including the muscles, kidneys, heart and brain. The brain gets less than 0.1% of the newly-absorbed iron.

As the iron-rich red blood cells die, they are broken down by specialized cells called macrophages. The iron from broken-down red blood cells is redistributed throughout the body, with most going back to the bone marrow and liver. It is this source of iron that is mainly utilized by the body to supply iron to other organs in the body. Again, a small percentage of that iron goes to the brain.

Understanding Low Iron Levels

When iron stores are low, the body's first response is to increase the percentage of iron going to bone marrow. Under severe iron-deficient conditions, as much as 99% of the body's iron will go to the bone marrow. This protective mechanism permits the body to continue making red blood cells by sacrificing iron distribution to other organs, including the brain.

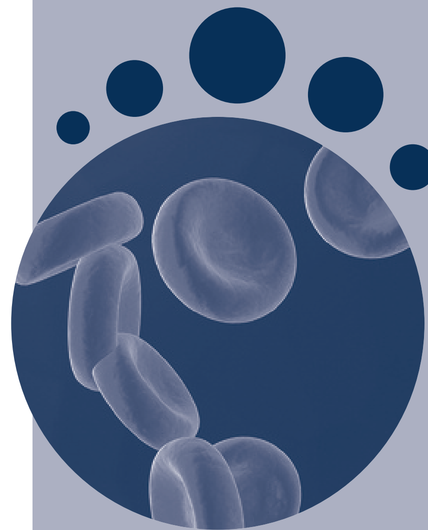
Animal studies have shown that low brain iron will directly or indirectly impact several systems in the brain, including the dopaminergic system. At baseline, dopamine levels vary significantly throughout the day, following the circadian rhythm, when dopamine levels are already lower at night and during sleep. Under low brain iron conditions, there is an additional decrease in the dopaminergic signal. A relative overall decrease in dopamine activity will have the greatest impact. Because of the circadian nature of RLS (worse at night and least likely to occur in the morning), a decrease in dopamine signaling as a result of low brain iron can exacerbate RLS.

Specific blood tests are used to determine body iron stores. Hemoglobin/hematocrit tests are the most commonly-requested measures, primarily to detect anemia (low red blood cell count). However, even in those RLS patients with severe iron deficiency, anemia is uncommon. Therefore, more direct measures of the body iron status is essential in evaluating any patient with RLS.

Complete Iron Measures

Serum ferritin level has been the standard measure for assessing the iron status of the body. However, it only directly reflects the iron stores in the bone marrow and the blood. The iron status of other organs (e.g., muscle, heart or brain) cannot be assumed to be the same as serum ferritin levels. Because infection and inflammatory processes can falsely elevate the serum ferritin level (i.e., the ferritin is no longer a reflection of the iron stores), it is necessary to wait at least six weeks after illness subsides before scheduling a ferritin test to get the true measure of body iron stores. Age is also a factor, since serum ferritin levels will increase with age and with declining kidney function. So, a fasting ferritin of 50 mcg/L in a 20-year-old woman is normal but should be considered abnormal in a 70-year-old woman.

A complete iron panel should include serum iron and ferritin level, total iron binding capacity and percent iron saturation. The complete iron panel will provide a broader understanding of the patient's iron status. Total iron binding capacity (TIBC) will also be affected by infection and inflammatory processes; so, like



Oral iron supplements are recommended when ferritin levels are less than 75 mcg/L.

Consider intravenous (IV) iron if 100 mcg/L level isn't reached.

Iron tests include:
- **serum iron and ferritin level**
- **total iron binding capacity (TIBC)**
- **percent iron saturation**

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ferritin, it is not a reliable marker for iron status under these conditions. Furthermore, serum iron levels increase significantly within 15 minutes of eating food and can vary by nearly 50% from morning to night. A dinner low in meat content the evening prior, followed by an early-morning blood test (i.e., before 9 AM) after fasting for at least 8 hours is recommended to provide a true picture of iron status. Also, if you are taking an iron supplement, as an iron pill or in combination with a vitamin pill, that should be stopped at least two days prior to the blood collection.

Dietary Sources of Iron

About 10% of the average daily dietary intake of iron (10-20 mg) is absorbed in the gastrointestinal (GI) tract. The same amount of iron in plant-based foods does not provide the same amount or type of iron found in animal proteins. Animal protein sources of heme iron, such a meat, fish and liver provide the most absorbable form of iron in the gut. Non-heme iron contained in beans, grains, fruits, vegetables and nuts are not as readily absorbed by the human GI tract.

Oral Iron

Based on current consensus reports, it is recommended to treat RLS patients whose ferritin levels are less than 75 mcg/L with iron supplements, with the goal of getting the ferritin above 100 mcg/L. Oral iron supplements with at least 60-65 mg of elemental iron should be used. To achieve maximum absorption, take the iron supplements on an empty stomach. To enhance iron absorption, take with 200 mg of vitamin C or with a beverage high in vitamin C such as orange juice; this is especially important if you are taking antacids or medications to treat acid reflux. It is essential to avoid calcium (dairy products, supplements, antacids), tea and coffee within two hours of taking iron supplements, as this will reduce iron absorption. To maintain the effectiveness of thyroid medications, avoid taking iron pills within four hours of thyroid medications.

Oral iron supplementation takes between three and nine months before many individuals obtain adequate stores. Recent research indicates that taking iron once per day is as effective as dosing twice daily, with marginal loss of therapeutic effect. An additional benefit of once-daily dosing is fewer adverse GI effects. Studies have shown that serum iron is redistributed to the brain to a much greater extent at night. Therefore, it has been recommended that the iron pill be taken in the evening as opposed to the morning.

An iron panel (serum iron, ferritin, TIBC and percent iron saturation) should be checked after three months. Remember to stop the iron pill two days before the blood is drawn. If the goals were not reached after three months, then consider an iron infusion. Once ferritin goals have been reached, further need for the iron supplementation will vary from individual to individual.

To determine the next step, stop the iron supplements and check a serum ferritin level in three and in six months to see if there is any indication that the ferritin level is dropping again. If the ferritin level is dropping after discontinuing the iron supplements, then some level of daily supplementation may be required in order to maintain iron levels within a clinically optimal range. If GI bleeding or menstrual issues are causing blood loss, then some level of iron supplementation should probably be continued.

Oral iron therapy should only be instituted under the care and supervision of a physician. Serial lab tests are required to determine therapy effectiveness and to monitor for iron overload.

Intravenous Iron

Intravenous (IV) iron should be considered if adequate ferritin levels are not achieved after 3 months on appropriate daily oral iron supplements. In two randomized, double-blind, placebo-control studies, patients with normal hemoglobin, ferritin less than 300 mcg/L and transferrin saturation of less than 45%, showed significant improvement in RLS symptoms after being administered 1,000 mg of iron intravenously. Therefore, treating RLS patients whose ferritin level is 100 mcg/L or less with intravenous iron may provide an alternative option to oral iron supplementation.

The consensus-based iron treatment guidelines for RLS include two first-line IV iron formulations: ferric carboxymaltose (Injectafer) and low molecular weight (LMW) iron dextran (INFeD). Both formulations pose a low risk for allergic reaction. Alternative IV iron formulations such as iron sucrose (Venofer), sodium ferric gluconate (Ferrlecit) and ferumoxytol (Feraheme) lack adequate clinical trials to verify their efficacy in treating RLS.

An important note: premedication with diphenhydramine prior to IV iron infusion should be avoided in RLS patients, as it known to aggravate or trigger RLS symptoms.

The iron infusion itself will cause an acute reactive increase in ferritin that is independent of the iron load. It may take up to six weeks for the ferritin to equilibrate. Furthermore, the iron infusion may take up to six to eight weeks to provide full benefits on the RLS symptoms. Therefore, an iron panel and clinic evaluation should be done about six to eight weeks post-infusion to establish the current iron status, to assess for any improvement in RLS and adjust medications as indicated. There is limited data on the value of repeated IV iron treatment in those who benefited from the initial treatment and who later present with worsening of RLS symptoms and a drop in iron levels. Further iron assessments and treatment decisions should be driven by the return or worsening of RLS symptoms.

Conclusion

Keeping the body's iron stores at an optimal level is a complex process involving blood tests and periodic re-evaluation of the RLS treatment plan. For individuals with RLS, it is important to work with a healthcare provider who understands the delicate relationship between iron and RLS in order to properly manage the disease.

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[1] Allen RP, Picchetti, D, Auerbach M, et al. 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 Medicine. 2018;41: 27-44. Open Access Article.

[2] O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994.23(3):200-203.

[3] Sun ER, Chen CA, Ho G, etal. Iron and the restless legs syndrome. Sleep Medicine. 1998. 21(4):371-377

The RLS Foundation is dedicated to improving the lives of the men, women, and children who live with this often devastating disease. Our mission is to increase awareness, improve treatments and, through research, find a cure for restless legs syndrome.

This publication has been reviewed and approved by reviewers from the RLS Foundation Scientific and Medical Advisory Board.