

Restless legs syndrome and iron metabolism

Clinical bottom line

There appears to be a strong link between decreased brain iron reserves, and impaired neurotransmitter function in part of the brain called the substantia nigra. This probably explains why dopaminergic substances and iron supplementation are effective for some people with RLS.

Background

Restless legs syndrome (RLS) is known to be more common in blood donors, in late pregnancy, and in end stage renal disease, when iron stores are depleted. More definitive links between RLS and iron metabolism are explored below. This article does not rehearse the complexities of iron metabolism, which are best found elsewhere [1].

RLS and blood or body iron

The possibility that RLS might be associated with iron metabolism has quite a long history. For instance, the observation that serum ferritin was lower in patients with RLS than in those without RLS suggested some link, albeit that the study had only 18 elderly patients [2]. The inverse correlation of severity of RLS with serum ferritin levels, and improved symptoms after two months of treatment with oral iron salts helped to underline any association.

There are other associations between iron and RLS. A blinded assessment of subjective and objective symptoms examined 27 patients aged 29-81 years, and

confirmed an inverse response between RLS severity and serum ferritin, with worse sleep in patients with lower ferritin levels [3].

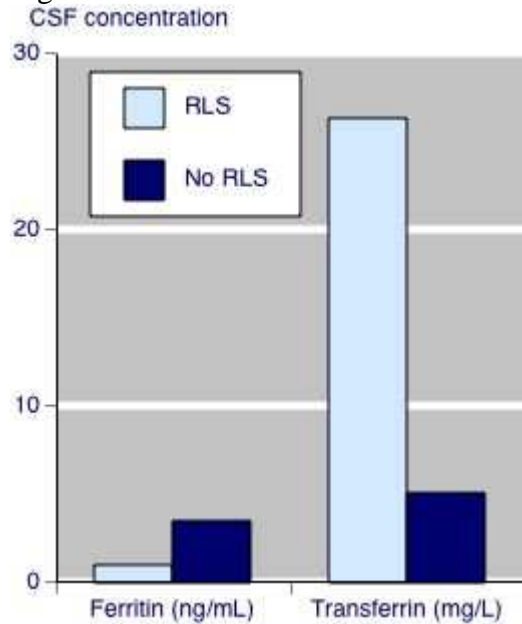
Serum iron levels, though, can be very variable. A more recent study of 16 patients with RLS and eight controls failed to find any difference in serum levels of ferritin, and had higher iron levels in patients with RLS [4].

Yet case reports also indicate that there may be an important link, at least in some people. For instance, three teenagers with RLS had low body stores of iron, though without marked anaemia. Oral iron therapy for four months restored body stores of iron, and improved their RLS symptom severity, with decreased sleep latency and periodic limb movements, and improved sleep efficiency [5].

RLS and brain iron

Lower levels of CSF ferritin, and higher levels of CSF transferrin (Figure 1) can be found in patients with RLS compared to normal controls [4]. An interpretation is that total brain concentrations of iron in patients with RLS are likely to be lower than those in patients without RLS. MRI measurements tuned to measure brain iron suggested that brain iron insufficiency was found in five RLS patients compared with five controls. The substantia nigra and putamen were implicated, with an indication that iron insufficiency was related to the degree of RLS severity [6]. Substantially decreased iron staining in the substantia nigra was confirmed in a histopathological study of the brains of seven subjects who had been diagnosed with RLS [7]. Electrophysiological changes in peripheral nerves, spinal cord and brainstem were normal in all 34 patients with iron deficiency anaemia, 14 of whom had RLS [8].

Figure 1: CSF ferritin and transferrin in the brains of patients with and without RLS



Thy-1 is a cell adhesion molecule playing a regulatory role in the release of neurotransmitters. In a study of brains of patients with RLS and without RLS, Thy-1 levels in the substantia nigra were half in patients with RLS compared with controls [9].

Comment

Local iron deficiency in the substantia nigra could impair dopaminergic function by limiting tyrosine hydroxylase activity or dopamine receptors or transporters. This indicates a possible link between decreased brain iron and responsiveness to dopamine and iron supplementation in RLS.

References

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