Restless legs syndrome (RLS) is the most common disorder of movement and quiet wakefulness, yet the pathophysiology of this common condition remains unclear. Studies have suggested a possible complex functional deficit of central nervous system dopaminergic, opiate and iron regulatory systems [1,2]. In addition, the role of the peripheral nervous system cannot be ruled out.

A cardinal feature of RLS is its diurnal or circadian variation, and occurrence of symptoms at night or in the evening is one of the key questions which make up the International Restless Legs Study Group (IRLSSG) criteria for diagnosis of RLS [3]. Iron deficiency continues to be a major cause of RLS and, as such, metabolic or functional abnormality of the central nervous system. Iron metabolism has been proposed as a fundamental abnormality that underpins the development of the diurnal symptom complex of RLS [2]. This theory has historical roots, as the medieval custom of ‘blood letting’ was thought to have a relationship with RLS, which Thomas Willis described. Willis is thought to have first described RLS in 1672 in the chapter titled ‘Instructions for curing the Watching evil’ in ‘London Practice of Physick’, published in 1685 [4].

In 1953, Nils Brage Nordlander, a contemporary of Ekbom, formally postulated that iron insufficiency caused RLS [5]. This differed from Ekbom’s emphasis on vascular problems being more important than low levels of iron in the pathogenesis of RLS [6,7]. Nordlander conducted an open-label study on 22 patients and used very large doses of intravenous iron to treat them. Twenty-one of these patients had complete relief from all their symptoms for several months. Ekbom himself described iron deficiency in 25% of patients with RLS and suggested that the lack of iron is a reason for the high incidence of RLS in pregnancy and treated patients with iron-substitution [7]. However, it has been pioneering work from Richard Allen, Chris Earley and colleagues that has further unraveled the hypothesis of iron deficiency and RLS in the last 5 years.

Between 2000 and 2003 Allen and colleagues published works indicating strong evidence to link iron deficiency with early-onset RLS. Studies on cerebrospinal fluid (CSF) showed decreased ferritin and elevated transferrin in patients with RLS in comparison with healthy controls [8]. Preliminary magnetic resonance imaging (MRI) studies also supported iron deficiency in RLS [9]. Subsequently, work from the same group has suggested that substantia nigra iron index is significantly lower in RLS compared to controls based on autopsy studies in four early-onset (onset <45 years) RLS and control brains [10,11].

Confirmation of the role of iron deficiency and occurrence of RLS in life would be useful if this could be replicated by in vivo techniques such as MRI. In this issue, Earley and colleagues report an elegant pioneering study using MRI to measure the iron concentration or ‘iron index’ in 10 brain regions in 39 controls and in 22 early-onset and 19 late-onset RLS subjects [12]. In line with autopsy studies, the mean iron index from the substantia nigra (SN) was significantly lower in the early-onset RLS compared to controls (t = 2.5, P = 0.016) but, interestingly, there was no difference in the iron index between late-onset RLS and controls. The authors also observed a significant negative Spearman rank correlation between SN iron index and the Johns Hopkins RLS severity (JHRLSS) for the control versus the early-onset RLS cohort (p = −0.32, P = 0.016).

Analysis of early- and late-onset RLS SN iron index showed no difference (P = 0.12) even though early-onset RLS showed a trend towards a relatively lower SN iron index than the late-onset RLS group. Exploratory analyses using individual t-test comparisons did not show significant differences (P < 0.05) in iron index between early-onset RLS and controls in any of the other nine brain regions.

The authors discuss the limitations of iron measurement using MRI and the fact that the ‘iron index’ is a measure of ferritin-bound iron and not the total tissue iron. MRI does not distinguish between the relative amounts of H- and L-ferritin in a tissue. This is relevant because autopsy studies in RLS indicated that in spite of low tissue concentration of iron and increased transferrin, it is the H-ferritin that is decreased but not L-ferritin which remains unchanged [10,11]. Normal L-ferritin levels may reduce the sensitivity of the MRI-determined measures to the disease severity. Furthermore, the iron index is unable to distinguish between the tissue site of storage of iron, glial versus oligodendrocytes. However, in spite of these limitations, this important and methodologically sound study does support the previous autopsy and CSF-based observations suggesting that at least in early-onset RLS, there appears to be consistent iron deficiency most obvious in the SN.
This observation will lead to two important strategies in relation to research and therapeutic advances in RLS. Firstly, MRI studies using a similar paradigm may be used more extensively in RLS and, secondly, this may help to determine and select patients who need more aggressive iron replacement.

References


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