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Original Article

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

Richard P. Allen [a, *], Daniel L. Picchietti [b], Michael Auerbach [c], Yong Won Cho [d], James R. Connor [e], Christopher J. Earley [a], Diego Garcia-Borreguero [f], Suresh Kotagal [g], Mauro Manconi [h], William Ondo [i], Jan Ulfberg [j], John W. Winkelman [k], On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

[a] Department of Neurology, Johns Hopkins University, Hopkins Bayview Medical Center, Baltimore, MD, USA
[b] University of Illinois College of Medicine at Urbana-Champaign and Carle Foundation Hospital, Urbana, IL, USA
[c] Department of Medicine, Georgetown University, Washington DC, USA
[d] Department of Neurology, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Republic of Korea
[e] Department of Neurosurgery, Penn State Hershey Medical Center, Hershey PA, USA
[f] Sleep Research Institute, Madrid, Spain
[g] Department of Neurology and the Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA
[h] Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano, Lugano, Switzerland
[i] Methodist Neurological Institute, Weill Cornell Medical School Houston, TX, USA
[j] Sleep Disorders Department, Capio Health Center, Örebro, Sweden
[k] Departments of Psychiatry and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Background: Brain iron deficiency has been implicated in the pathophysiology of RLS, and current RLS treatment guidelines recommend iron treatment when peripheral iron levels are low. In order to assess the evidence on the oral and intravenous (IV) iron treatment of RLS and periodic limb movement disorder (PLMD) in adults and children, the International Restless Legs Syndrome Study Group (IRLSSG) formed a task force to review these studies and provide evidence-based and consensus guidelines for the iron treatment of RLS in adults, and RLS and PLMD in children.

Methods: A literature search was performed to identify papers appearing in MEDLINE from its inception to July 2016. The following inclusion criteria were used: human research on the treatment of RLS or periodic limb movements (PLM) with iron, sample size of at least five, and published in English. Two task force members independently evaluated each paper and classified the quality of evidence provided.

Results: A total of 299 papers were identified, of these 31 papers met the inclusion criteria. Four studies in adults were given a Class I rating (one for IV iron sucrose, and three for IV ferric carboxymaltose); only Class IV studies have evaluated iron treatment in children. Ferric carboxymaltose (1000 mg) is effective for treating moderate to severe RLS in those with serum ferritin <300 μg/l and could be used as first-line treatment for RLS in adults. Oral iron (65 mg elemental iron) is possibly effective for treating RLS in those with serum ferritin ≤75 μg/l. There is insufficient evidence to make conclusions on the efficacy of oral iron or IV iron in children.

Conclusions: Consensus recommendations based on clinical practice are presented, including when to use oral iron or IV iron, and recommendations on repeated iron treatments. New iron treatment algorithms, based on evidence and consensus opinion have been developed.

* Corresponding author. Fax: +1 410 550 3364.
E-mail address: richardjhu@mac.com (R.P. Allen).

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1. Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a common neurological disorder, which significantly impacts quality of life, sleep, and health [1,2]. There is substantial evidence implicating brain iron deficiency in the pathophysiology of RLS [3,4], and current RLS treatment guidelines recommend the assessment of iron status and iron treatment when peripheral iron levels are low [5–8]. In recent years there has also been an increase in the number of scientific and clinical studies on the oral and intravenous (IV) iron treatment of RLS and periodic limb movement disorder (PLMD). In order to assess these data, the International Restless Legs Syndrome Study Group (IRLSSG) formed a task force to review these studies and provide, in this paper, updated evidence-based and consensus guidelines for the iron treatment of RLS in adults, and RLS and PLMD in children.

2. Iron regulation pertinent to understanding the role of iron treatment in RLS

Before establishing iron treatment guidelines for RLS, it is first necessary to recognize several unique features of iron biology and homeostasis, which affect treatment goals, methods of delivery, treatment response times, and the need for repeated treatment.

2.1. Iron biology

Iron in biological material exists in one of two forms: ferric (Fe^{3+}) and ferrous (Fe^{2+}), the latter being the most reactive (for a review see, Aisen et al. [9]). Iron transported in blood is primarily bound to transferrin, while cellular iron is stored primarily in the large globular protein, ferritin [10]. Serum ferritin appears to be secreted mostly by monocytic/macrophage cells [11] and may function to provide high volume iron loads to selected organs, such as the brain, independently of the transferrin-based iron transport system [12,13]. Serum ferritin, which is usually a reasonable measure of erythron[1]/macrophage iron status, is commonly used to guide oral iron therapy for iron deficiency (ID) anemia [14]. However, as an acute phase reactant, serum ferritin increases independently of iron status with any level of inflammation [14], often returns to normal range at 4 weeks but may remain elevated for more than 5 weeks after onset of inflammation [15,16]. Serum ferritin also increases, independently of iron status, with age and decreasing glomerular filtration rate [17,18]. While adequate body iron levels are required to support essential functions in all cells, iron overload causes serious toxic responses in cells and organs. Thus, iron homeostasis is highly regulated [10].

2.2. Iron homeostasis

Iron regulation in humans relies mainly on recycling body iron and controlling iron uptake (see reviews [10,17,19]). Approximately 10% of the usual daily 10–20 mg of dietary oral iron consumption is absorbed into the body. Dietary iron is actively controlled at the level of the intestinal epithelium and vascular endothelium. Once in the blood, the vast majority of iron (75% or more) goes to the erythron for red blood cell (RBC) production, with about 10–20% going to iron storage pools (mostly to liver, reticuloendothelial system [macrophages] and muscle). The macrophage is the primary source of iron, which is recycled to other organs, including brain, whether obtained directly from the blood or from iron recycled from senescent red blood cells [10]. Only 5–15% of newly absorbed iron (0.5–1.5% of the iron consumed orally), is available for transport to organs such as in the kidneys, heart or brain [10,17]. The rate of iron absorption is primarily regulated by hepcidin that serves to block the uptake of iron from the gastrointestinal mucosa, macrophages, and from the liver into the blood [20]. Increases in blood or liver iron stimulate the production of hepcidin, as does an increase in inflammatory factors [20]. This causes a reduction in gastrointestinal iron absorption, thereby limiting the utility of oral non-heme iron in further increasing body iron stores (see Fig. 1) [10].

Iron homeostatic mechanisms are, however, organ specific and under the control of complex genetics [21–23], this complicates the determination of the iron status of an organ. Iron status first became clinically relevant as an indication of anemia, and later, to a lesser extent, iron overload. Efforts to produce reliable measures of iron status have been exclusively based on the iron status of the erythron [18]. The clinical use of the term “iron deficiency” (ID) is based on bone-marrow-determined iron concentrations with hemoglobin (Hgb) and other serum measures of iron status developed as correlates of bone-marrow iron. Thus, clinical measures of body iron stores, including serum iron, transferrin saturation, and serum ferritin, reflect primarily the iron status of the erythron [18]. When ID is defined by a conservative serum-based, bone-marrow-defined measure (e.g., transferrin saturation <16%), then the prevalence of ID, with or without anemia, is reported to be 16% in menstruating women in the USA [24]. However, if liver iron stores are used, autopsy data indicate that ID among menstruating women is 50% in the USA [25]. Serum measures and criteria used in clinical practice to define “iron deficiency” provide a good to very good measure of the iron status in the erythron, but serum measures have not been validated as measures of iron status in other organs.

Iron homeostasis in the brain is regionally regulated through an interaction of local cellular energy demand and blood brain barrier accessibility [26]. All of these mechanisms are subservient to complex genetic determinants, circadian processes and, most importantly, the availability of iron in the body [27–29]. Iron is actively taken up into the brain on a minute by minute basis [30], even in areas with apparently adequate iron stores [28]. This “demand” for more iron appears to be under the influence of circadian dynamics [28,31] and thus presumably follows circadian fluctuations in energy/metabolic demand [32]. Despite the existence of general concepts of the mechanisms involved in homeostatic regulation of iron in the brain, there are no adequate measures of local cellular brain iron requirements, and no measure on an individual-by-individual basis of how any one of these mechanisms or genetic factors affect brain iron stores. Animal data have shown that serum iron and related indices reflect brain iron status very poorly, with genetic variations producing large differences in the blood–brain iron regulation for individual animals [27]. Measures of iron-related serum factors provide information about their primary source: erythron, macrophage, and liver, but bear minimal, if any, relation to regional brain iron. Extrapolating from animal data it can be said for humans that (1) systemic ID will reduce brain iron in select regions in some individuals, (2) some individuals with normal serum iron levels may still have relatively insufficient regional brain iron, and (3) serum measures of peripheral iron status are unlikely to be related to regional brain iron, and thus poorly related to RLS expression.

2.3. Rationale for iron treatment of RLS

Several studies have shown that lower ferritin is associated with increased RLS severity [33,34]. Severe ID to the point of anemia is

[1] Erythron is the name given to the collection of all stages of erythrocytes throughout the body and this includes the developing precursors in bone marrow and the circulating mature erythrocytes in the peripheral blood, therefore erythron is the entirety of erythroid cells in the body.