

# IRON SUPPLEMENTATION FOR PEDIATRIC RESTLESS LEGS SYNDROME

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Restless legs syndrome (RLS) in children is a neurological, sensorimotor, genetically-determined disorder, causing dysesthesias that are troublesome particularly in the evening, improve with movement, and can be a cause of sleep onset and sleep maintenance insomnia.<sup>1,18-23,31,54,56,57,58</sup> It can also cause non-restorative sleep and daytime sleepiness. RLS has a reported prevalence of 10% in adults and 2% in children.<sup>18</sup> Iron deficiency is the most common environmental trigger for RLS.<sup>55</sup> Sleep hygiene and oral iron supplementation are first line treatments for RLS in children (Simakajornboon).<sup>1,49</sup> The literature to date suggests children may benefit from a trial of iron therapy to increase serum ferritin to 50 ug/L,<sup>1</sup> the level in adults associated with improved RLS.<sup>2,3</sup>

Children with RLS may or may not have systemic iron deficiency (blood test screen). Well documented evidence supports the concept that brain iron deficiency is a risk factor for RLS.<sup>31-36</sup> The exact mechanism through which this risk factor works has not yet been elucidated, although iron seems to be needed for dopamine system function.<sup>36</sup> Whether one can achieve a change in brain iron status by increasing systemic iron is unclear.<sup>37</sup> However, based on limited but remarkable data<sup>38</sup> and clinical experience<sup>25</sup> in adults with RLS, the literature states that serum evaluation for iron deficiency, by testing serum ferritin and transferrin saturation, is a standard part of the initial medical assessment of RLS.<sup>24-30</sup> For adults, it is recommended that any patient with a ferritin less than 50 ug/L be started on oral iron replacement therapy, with vitamin C to enhance absorption,<sup>36</sup> to increase serum ferritin to at least 45 to 50 ug/L.<sup>2,25,52</sup> Current, albeit limited, evidence<sup>43-48</sup> for pediatric RLS suggests that achieving and maintaining serum ferritin above 50 ug.L in children and adolescents may be of benefit for their sleep.<sup>42</sup>

To prevent iron overload, screening for hemochromatosis should include taking a personal or family history of hemochromatosis or unexplained liver disease, and measuring transferrin saturation and serum ferritin before starting iron therapy<sup>9,39,40</sup> and every 3 months after starting iron therapy.<sup>25,30,39,40</sup> Transferrin saturation (saturation index) >50% and/or elevated serum ferritin are highly indicative of hemochromatosis in children.<sup>41</sup> In the absence of disorders of iron homeostasis such as hemochromatosis,<sup>4</sup> which place children at risk for iron overload, oral iron supplementation is considered a safe treatment. Iron absorption is reduced at higher ferritin concentrations, countering further iron accumulation in the body above physiologic limits.<sup>5</sup>

## HOW TO SCREEN FOR IRON DEFICIENCY

### **Ferritin**

### **Iron Panel (iron, TIBC, and saturation index)**

### **CBC**

The serum ferritin level is the best screening measure of iron stores.<sup>6,7</sup> A serum ferritin level < 12 ug/L is diagnostic of systemic iron deficiency,<sup>6</sup> and between 10-20 ug/L is indicative of depleted iron stores. The cut-off values used for low ferritin differ across centers (< 6 ug/L to < 22 ug/L).<sup>6,8-12</sup> In Edmonton, the lab results form uses 12 ug/L as the cut-off value for low serum ferritin. Published mean ferritin values are higher (eg 34 ug/L as reported by The World Health Organization<sup>86</sup>). However, ferritin can be an acute phase reactant; a result in the normal range may be falsely elevated due to conditions such as infection or inflammation.<sup>6</sup> When ferritin is falsely elevated, concentrations of less than 50-60 ug/L could indicate depleted iron stores.<sup>7,14</sup>

Because a normal serum ferritin value does not exclude iron deficiency, measuring multiple markers can detect iron deficiency more accurately.<sup>6</sup> The Centers for Disease Control and Prevention (CDC)<sup>9</sup> has defined iron deficiency based on at least 2 abnormal values out of 3 tests of iron status (serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin).<sup>8</sup> Abnormality of the other markers theoretically reflect the 3 stages of iron deficiency (see table below).<sup>6</sup>

**Stage I:** Storage iron depletion (↓serum ferritin).<sup>6</sup> Iron deficiency usually progresses slowly. Once the iron stores are completely exhausted, the second stage occurs.<sup>6</sup>

**Stage II:** Iron-deficiency erythropoiesis (↓transferrin saturation, ↓iron, ↓MCV, ↑total iron binding capacity (TIBC), ↑erythrocyte protoporphyrin).<sup>6</sup>

**Stage III:** anemia (↓hemoglobin).<sup>6</sup> Most children with iron deficiency do not have anemia.<sup>6,8</sup>

However, even when using multiple markers, screening for iron deficiency in its early stages can be difficult because the other marker results can be non-specific<sup>6,9</sup> and because the three stages may not be distinct, resulting in overlapping test results.<sup>7</sup> For example, iron deficiency cannot be excluded if the results are normal for TIBC, erythrocyte protoporphyrin, and MCV.<sup>6</sup> Erythrocyte protoporphyrin is an expensive test. Note that, for our labs in Edmonton, to measure transferrin saturation, you need to order an iron panel ([which includes iron, TIBC, and saturation index](#)).

When systemic iron deficiency is found, it is important to remember that investigations into possible causes of the iron deficiency should be pursued,<sup>7</sup> such as dietary iron insufficiency (the most common cause in children)<sup>17</sup> or celiac disease.<sup>50,51</sup>

## **HOW TO PROVIDE IRON TREATMENT FOR PEDIATRIC RLS**

Dose: There is no published recommendation on dose of iron treatment for pediatric RLS. The recommended dose of iron supplement for treatment of pediatric iron deficiency is 4.5-6 mg/kg elemental iron/kg/day.<sup>7</sup> That is what we use to treat RLS when serum ferritin is < 50 ug/L.

To enhance absorption, iron could be taken with a source of vitamin C (such as orange juice). Absorption is inhibited by food such as cereals and milk.<sup>7</sup>

Duration: There is no published recommendation on duration of iron treatment for pediatric RLS. The duration of therapy for non-anemic iron deficiency is 3-6 months.<sup>7</sup> We usually treat for 3 months and then reassess lab results and clinical response to treatment. RLS severity increases with age, into adulthood.<sup>53</sup> At disease onset, symptoms are mild, have variable frequency (eg once per week or month, or daily),<sup>54</sup> and are punctuated by asymptomatic periods of variable duration.<sup>53</sup>

## **HOW TO MONITOR FOR IRON OVERLOAD**

Measure transferrin saturation and serum ferritin before starting iron therapy<sup>9,39,40</sup> and every 3 months after starting iron therapy.<sup>25,30,39,40</sup>

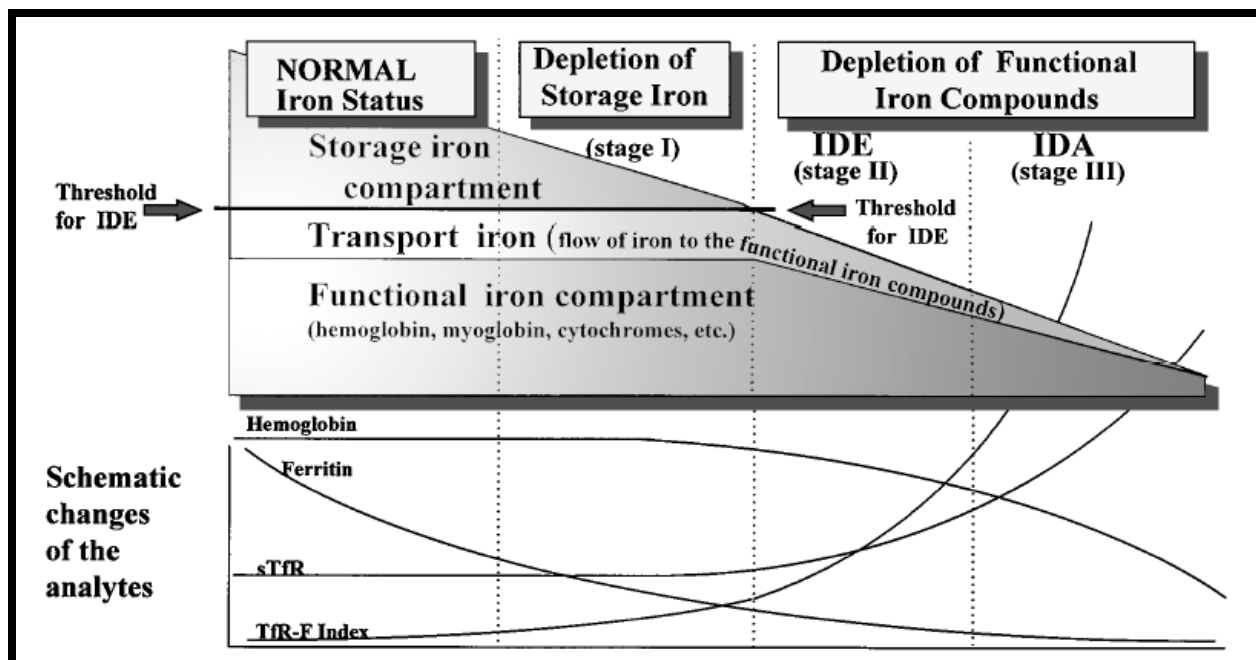
Transferrin saturation ([saturation index](#)) >50% and/or elevated serum ferritin are highly indicative of hemochromatosis in children.<sup>41</sup>

Elevated ferritin values, according to the reference range used by the University of Alberta Hospitals laboratory,<sup>59</sup> are:

Age 6 months to 14 years 11 months: >140 ug/L

Males age 15 years and older: > 250 ug/L

Females age 15 years and older: > 120 ug/L



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