



2018 Webinar Series

Iron Biology: What We Should Know When Managing Restless Legs Syndrome

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Norlander 1953

- First to report the benefits of IV iron treatment on RLS symptoms in those with ID anemia
- First to report the benefits of IV iron treatment on RLS symptoms without ID anemia

Iron status and RLS

- **Ekbom (1960):** Increased prevalence of ID in RLS population (15-25%)
- **O'Keefe (1992):** low ferritin levels (4-50 ug/l) are associated with increased RLS severity
- **Sun (1997):** lower ferritin levels (5-250 ug/l) are associated with increased RLS severity and decreased sleep efficiency.

Lower iron stores are associated with increase severity of the RLS and decreased sleep quantity/quality

But does lower iron levels **cause RLS**

The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia

Allen et al. Am J Hematology 2013

- Single hematology Clinic
- Consecutive new patient with IDA over 1 year
- Cambridge-Hopkins Diagnostic questionnaire



The prevalence of RLS in a ID anemia population

Diagnosis	Sample Size (% of total)
All patients	251
All RLS	79 (31.5%)
RLS “sufferers”	60 (24%)
Not RLS	123 (49%)
Uncertain	49 (19.5%)

Prevalence of RLS in USA population 5%

Prevalence of RLS “sufferers” in USA population 3%

Norlander 1953

After successfully treating non-anemic RLS patients with IV iron, he one postulated:

“it is possible...that there can exist an iron deficiency in the tissues in spite of normal serum iron”

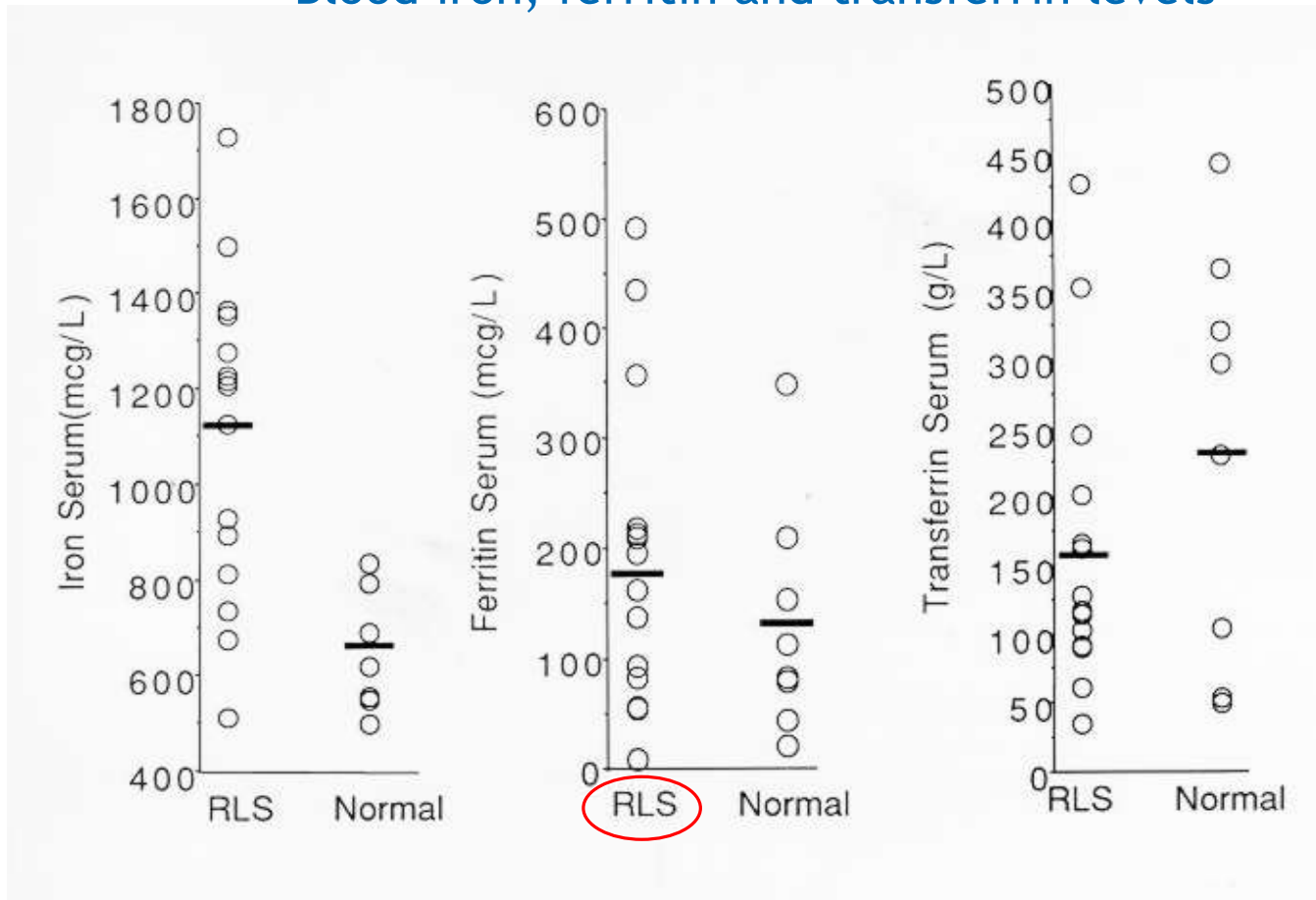
Implication: Iron homeostasis is tissue-specific

Could the brain have low iron despite normal serum values?

Brain Iron Homeostasis in RLS



Blood iron, ferritin and transferrin levels

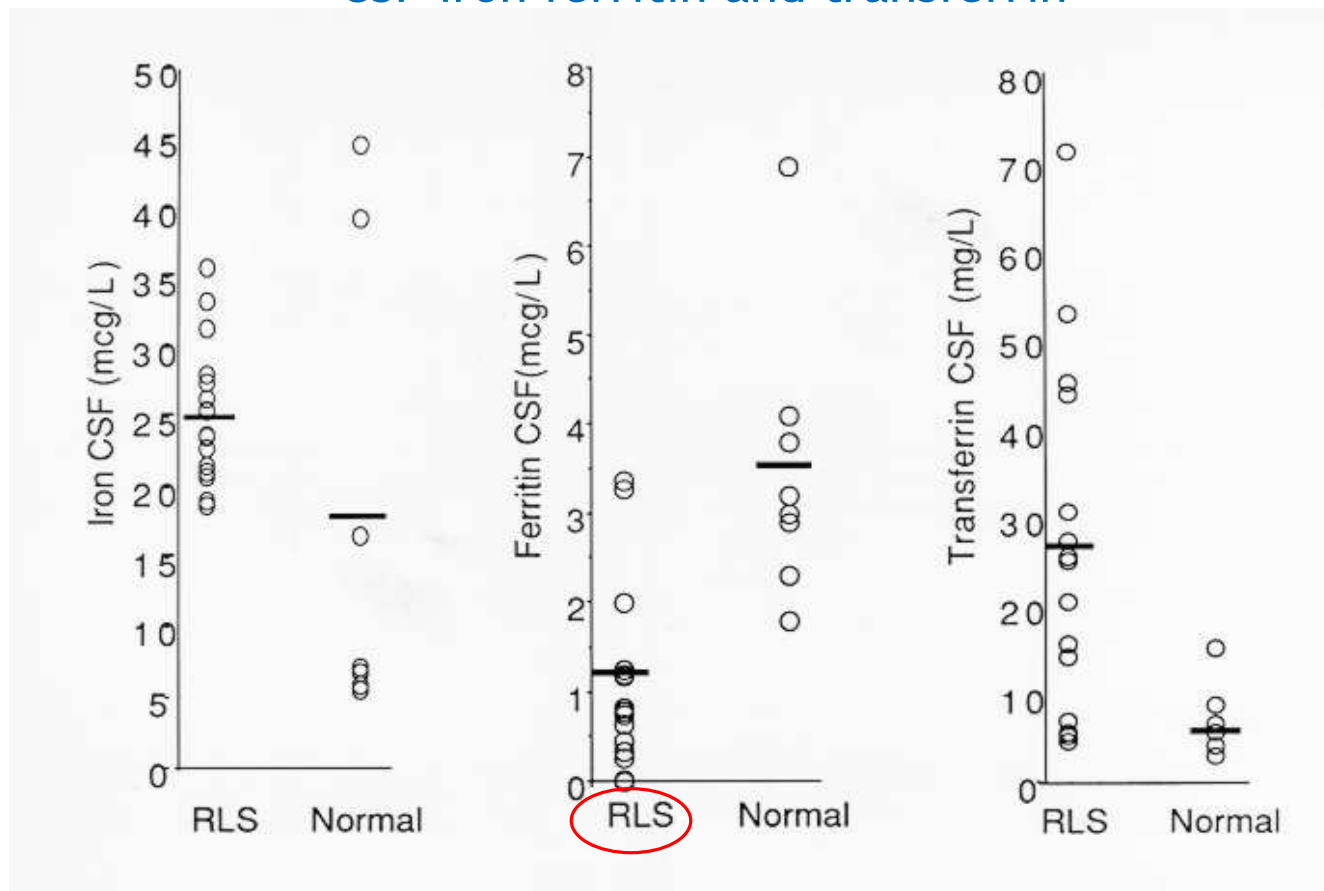


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CSF iron ferritin and transferrin



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Cerebrospinal fluid studies in RLS

5 Studies

- Earley 2000, 2005; Mizuno 2005; Clardy 2006a, 2006b

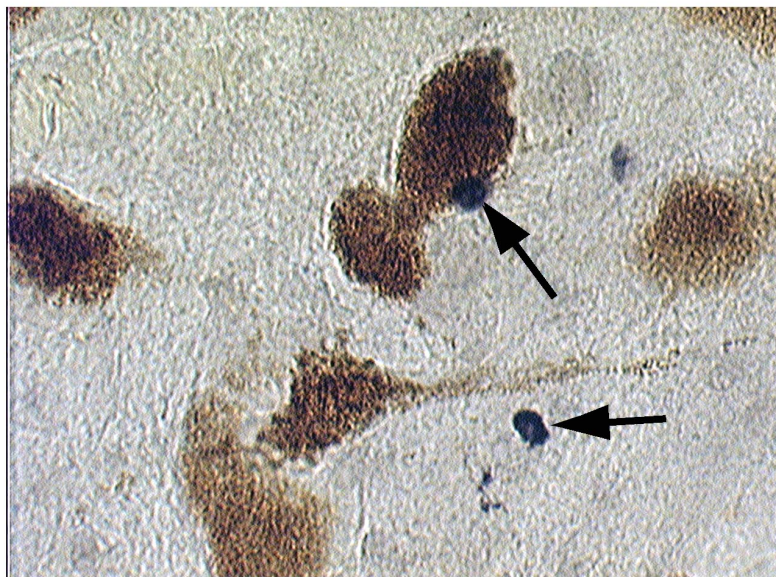
Overall conclusion

- The findings are consistent with CNS iron insufficiency

H-Ferritin in the Substantia Nigra



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Brain autopsy studies

5 Studies

- Connor et al 2003, 2004, 2011; Snyder et al 2009; Clardy et al 2006

Regions Investigated

- Substantia nigra, putamen, microvasculature, choroid plexus, white matter

Overall conclusions

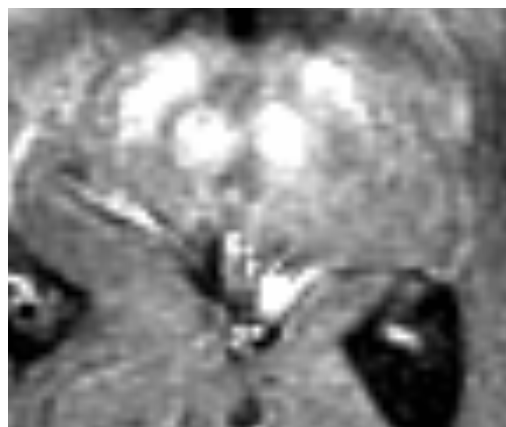
- RLS is association with altered CNS iron homeostasis leading to cellular iron insufficiency

Brain iron concentrations as determined by MRI

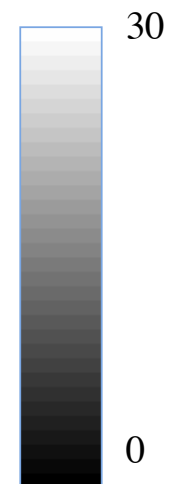
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Normal



R2* (sec⁻¹)



R2* images in a 70 year old RLS patient and a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both **red nucleus** and **substantia nigra**.

MRI studies in RLS

8 Studies

- Allen 2001; Earley 2006; Lee 2007; Godau 2008; Knake 2010; Margariti 2012; Rizzo 2013; Moon 2015

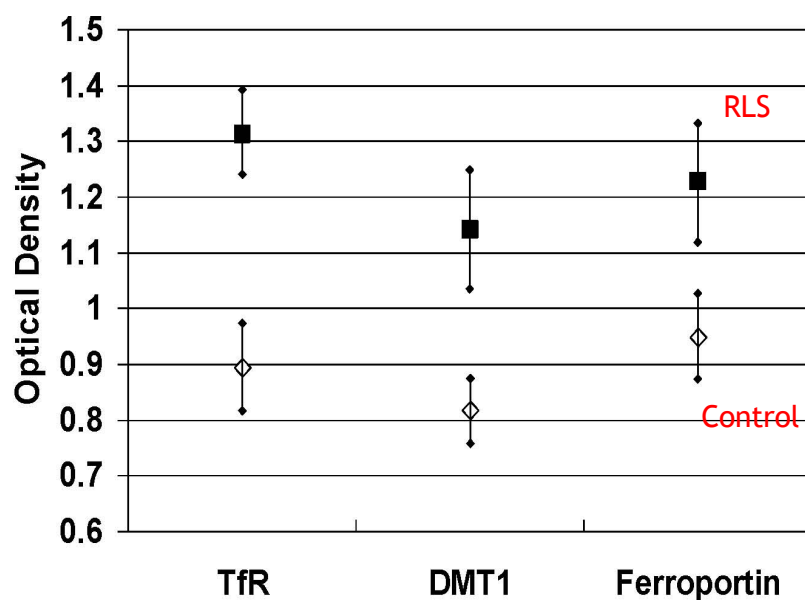
Regions Investigated

- Substantia nigra, red nucleus, putamen, GP, caudate, thalamus, pons, dentate

Overall conclusion

- The findings support the concept of a relative decrease in the brain iron with decreases in the SN being the most consistent finding

Concentration of iron management proteins in lymphocytes from RLS and control women



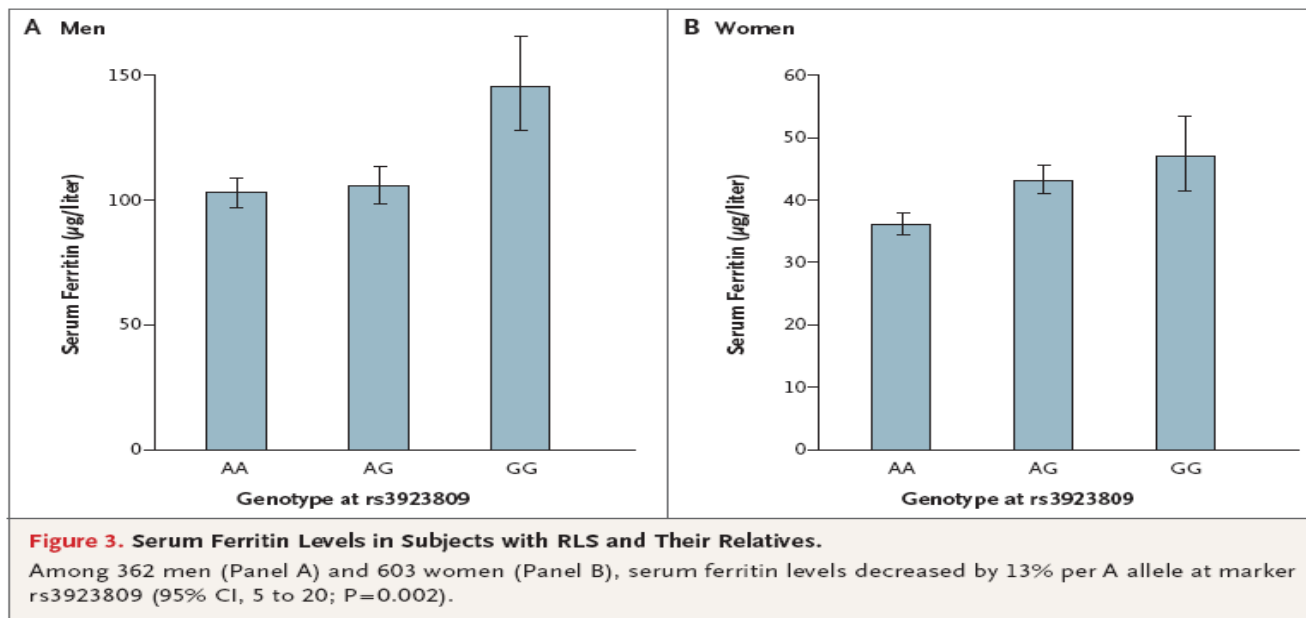
Earley et al, 2008

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Association between serum ferritin and BTBD9 allele



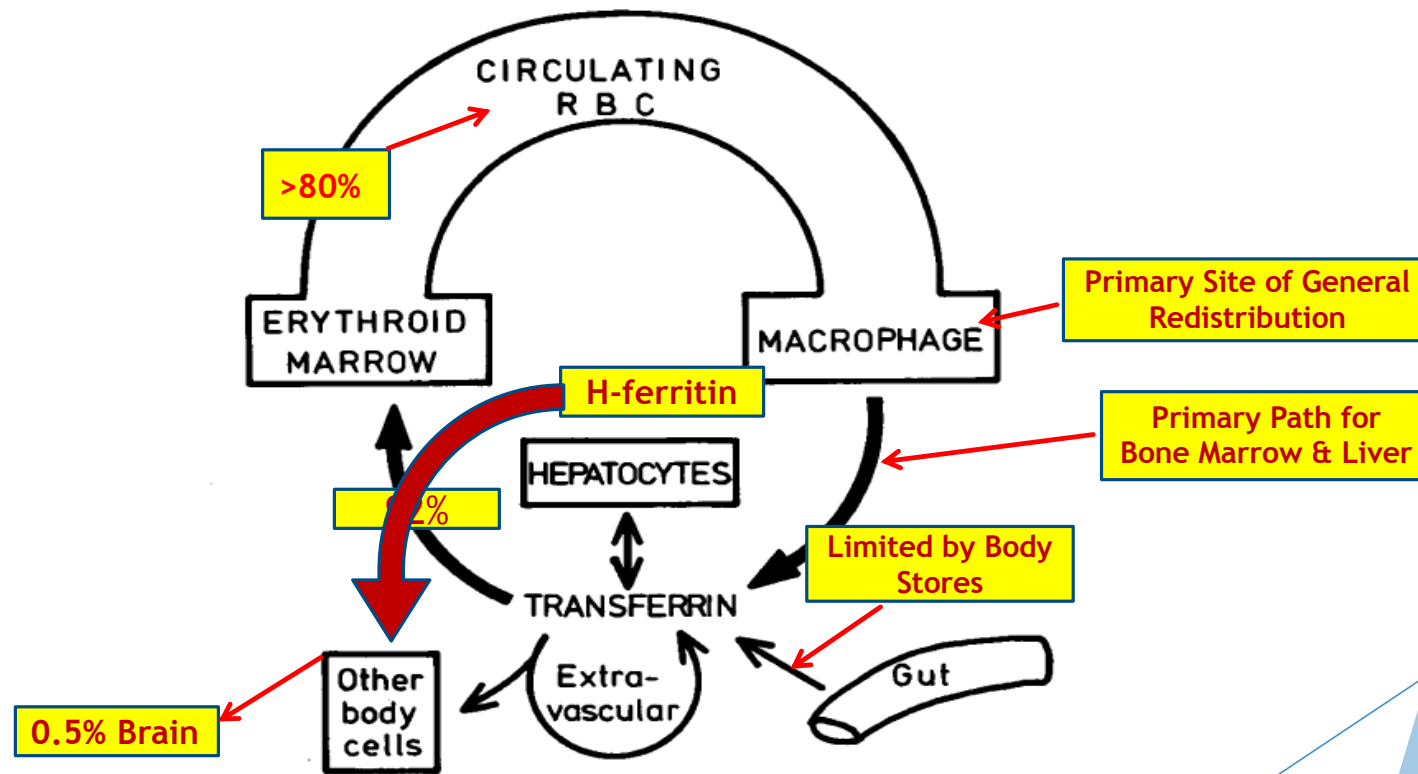
(Stefansson et al NEJM 2007)

Take Home Message

1. Iron deficiency conditions (IDA and pregnancy) are a major environmental trigger for RLS
2. RLS is associated with altered iron homeostasis involving brain, vasculature and lymphocytes
3. There is a disconnect between serum-determined levels of iron and brain cellular iron levels in many RLS patients
4. Cellular iron insufficiency in the substantia nigra has been the most consistent finding and at least represent a viable surrogate for altered iron homeostatic mechanisms in RLS

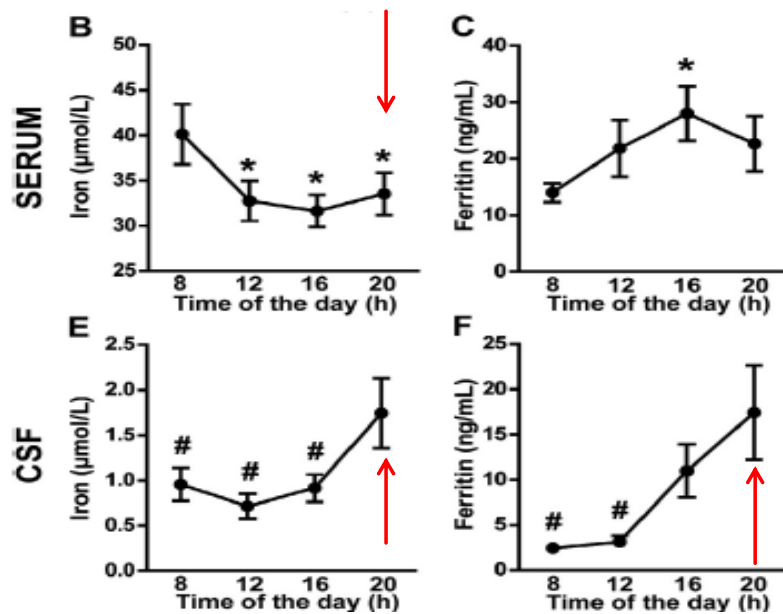
Understanding iron homeostatic mechanisms under normal and iron insufficiency condition may be pertinent to understanding and managing RLS

Basic Iron Biology - Internal Distribution of Iron



Circadian changes in primate serum and CSF iron and ferritin

Hyacinthe et al
Neuroscience 2015

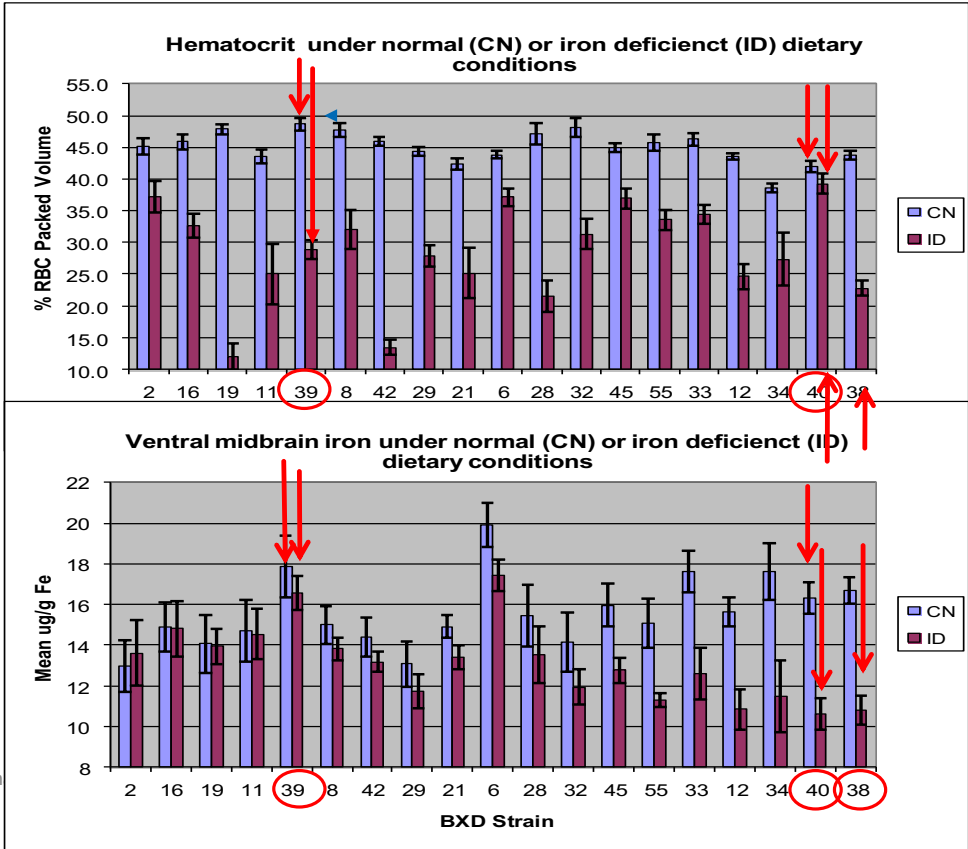


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Hemoglobin and VMB iron across recombinant inbred mice strains (C57BL/6J X DBA/2J (BXD))



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Take Home Message

1. Iron homeostasis involves a complex set of genetic interactions that appear to be tissue specific and lead to individual variability in tissue iron concentrations.
2. Serum measures of iron status are, at best, fair guide to the iron status of the bone marrow and are poor guide to the iron status of brain
3. Iron homeostasis is significantly influenced by circadian mechanisms
4. Circadian change in iron homeostasis may be relevant to the timing of iron treatment in RLS

The Role of Iron Supplementation in RLS Patients



Oral iron therapy

325 mg ferrous sulfate + 100 mg Vit C - BID

Davis 2000- R/DB, 14 weeks; ferritin 134 ug/l.

No difference in RLS BUT no difference in ferritin.

Wang 2009-R/DB, 12weeks; ferritin 15-75 ug/l.

Significant improvement in RLS and in ferritin

Intravenous iron formulations

1. Iron sucrose (Venofer) - 2-4 hr half life
2. Ferric gluconate (Ferrlicit) - 4 hr
3. LMW-iron dextran (INFeD) - 18-24 hr
4. **Ferric carboxymaltose (Injectafer)** - 24 hr
5. Ferumoxytol (Feraheme) - 16-20 hr
6. Iron isomaltoside (Monofer) - 14-18 hr

The type of IV iron formulation that is used may be more relevant to treating RLS than to treating IDA

Clinical efficacy of ferric carboxymaltose treatment in patients with restless legs syndrome

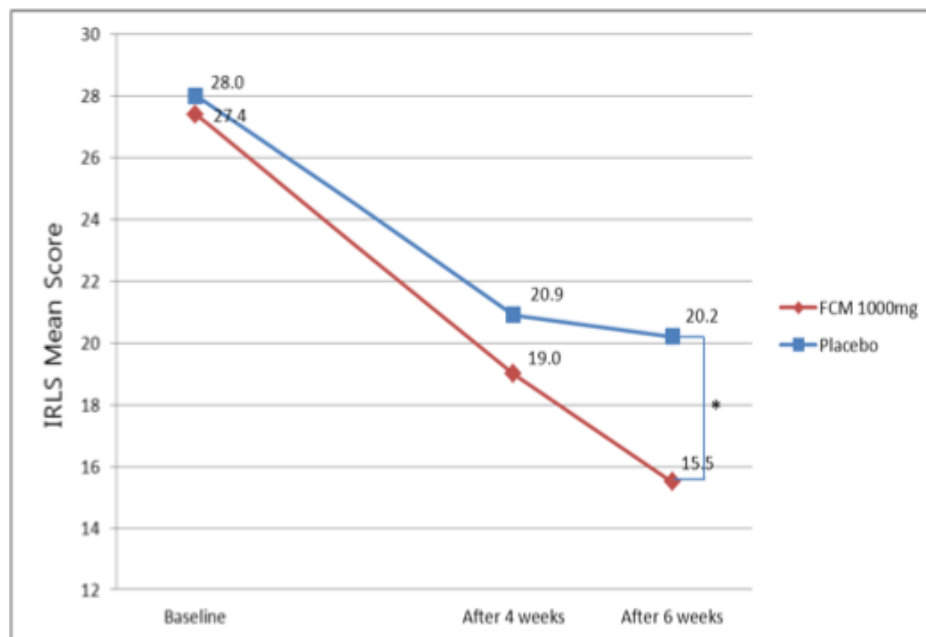
(Cho et al 2016)

Randomized, double-blind, placebo-controlled trial

Korean population on treatment or seeking treatment for RLS

32 received 500mg x 2 FCM 5 days apart vs. 32 placebo

Mean IRLS scores at baseline, Week-4 and Week-6 for the FCM and Placebo groups

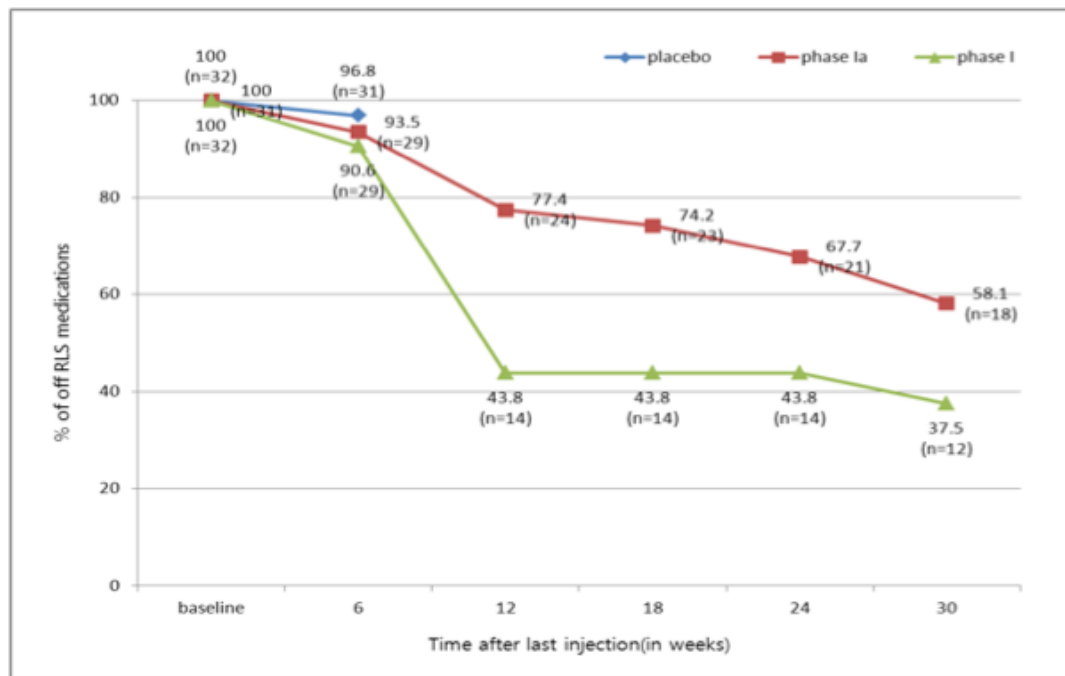


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The percent (absolute number) of subjects over time who remained off RLS medications after receiving FCM in either the Phase I or Ia



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Intravenous iron therapy for RLS

Serum ferritin < 100 ug/l

Iron infusion - 1000 mg

Maximal effectiveness at 6 weeks post infusion

Repeat iron panel at 8 and 12 weeks post infusion

Establish clinical status at 8 weeks after infusion and then reassess for stability at 12 weeks

If patient responded to the initial Infusion, then repeat IV iron when RLS worsens if associated with drop in iron indices

Commonly used serum indicators of iron deficiency

Hemoglobin <12 women and <13.5 men

Poorest indicator of iron status

Ferritin < 18-30 ng/ml

Increases with ↑ inflammation, ↑ age, and with ↓GFR

TIBC > 400

Decreases with ↑ inflammation and with ↓GFR

AM fasting iron <60-65

Meat for dinner will ↑ AM iron

Percent iron saturation < 16-18%

Calculated from serum iron +TIBC

> 45% hemochromatosis??

Patient

Male; age 67; RLS x 20 years; IRLSS=30

Early morning overnight fasting labs

- ▶ Hemoglobin=13.5
- ▶ Serum iron=65
- ▶ Ferritin=65
- ▶ TIBC=395
- ▶ Percent saturation=20

Should iron therapy be your first treatment choice for managing his RLS?



Question and Answer

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