Brain iron, Iron Treatment and PLMS

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Background

Reduced brain iron is the best-established biological abnormality in restless legs syndrome (RLS). Moreover, it is one that could potentially be corrected by appropriate iron treatment. This is the only RLS treatment reducing an established biological abnormality of RLS, Other treatments are essentially palliative. Thus this treatment has the potential of producing longer lasting results. Planning this treatment should be based on understanding the biology of iron: 1) Iron status is regionally regulated in the brain and RLS has both some general but more regionally specific brain iron deficits. 2) Regional brain iron deficits relate to specific RLS symptoms 3) 24 hour changes in brain iron reflect dynamic brain iron flux; 4) Peripheral iron status priority alters brain iron availability – thus producing 2 very separate types of brain iron relation to RLS: iron deficient anemia vs. normal peripheral iron and 5) Iron treatments can be very safe.

The new data from two separate labs indicate that both the thalamus and the substantia nigra are primary areas of significance for brain iron changes in RLS. These regional areas are expected to have differing relation to RLS symptoms. Our recent data document that substantia nigra iron levels relate well to the periodic limb movements in sleep for RLS patients. This is consistent with the pediatric data on benefits of Iron treatment.

Brain iron has a 24-hour cycle indicating a dynamic flux of iron. The older concept of the brain accumulating and then storing the iron is not correct. This flux appears to involve dynamic peripheral – central iron exchange.

Iron treatments must be based on the biology of iron management. Iron regulation in the body favors maintaining erythropoiesis and less than 1% is available for macrophages

and transport to the brain. There are two very different conditions for iron treatment in RLS.

1) RLS occurring with iron deficiency anemia and peripheral iron deficiency without anemia. The peripheral iron measures are significant in these cases with lower iron status relating somewhat to disease severity and recovery of normal iron status associated with rapid reduction often remission of RLS. It is assumed in these cases that the brain iron deficiency occurs because of lack of peripheral iron needed to maintain the dynamic iron flux supporting adequate brain iron.

2) RLS occurring without any peripheral iron deficiency. In these cases the brain iron deficiency is not closely related to the peripheral iron status. But even in these cases for some a very large increase in peripheral iron via IV iron may lead to improved symptoms presumed to occur because of reduced brain iron. There are two important differences between this type of RLS and RLS related to peripheral iron deficiency. First, the response to IV iron is usually delayed for a few weeks, with maximum response occurring at about 6 weeks after treatment. This may reflect the cycling of the added iron through peripheral stores eventually making it available to support the brain iron flux. Second, there is no relation to peripheral iron measurements. Thus the treatment cannot be restricted to those with certain peripheral iron measurements except as needed to ensure safety of IV iron. In particular, iron treatment should not be given for safety reasons to anyone with transferrin saturation > 45%. It is also common to not give IV iron treatment if serum ferritin > 300 mcg/l. Aside from these safety issues there is no value in looking at the peripheral iron measures for predicting response or deciding whether or not to treat. Note though, that the values need to be obtained for safety and also to identify those with RLS associated with peripheral iron deficiency.