Ironing out fatigue

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Women who are not anemic but who suffer from fatigue may benefit from iron supplementation. In this issue of Blood, Krayenbühl et al provide strong evidence that women complaining of fatigue who were not anemic but who had reduced or absent iron stores were symptomatically improved after receiving parenteral iron.1 Given the numbers of women who are iron deficient, the findings could find broad application, but work needs to be done to refine the approach to this common problem.

Iron deficiency affects many cellular systems beyond hemoglobin formation, including DNA synthesis, the immune system, and mitochondrial electron transport. Physiologists have long recognized that cellular iron deficiency contributes to reduced enzymatic activity in mitochondrial electron transport systems and impaired muscle function in experimental animals2,3 and that, with iron treatment, muscle function is restored. Iron deficiency has also been linked to cognitive impairment and fatigue, although the associations are not robust.4 Not surprisingly, the beneficial effects of iron supplementation in subtle conditions, such as fatigue, have been difficult to prove, although several earlier clinical studies reported positive results.5,6 These studies had inherent problems, making it difficult to tease out the placebo effect or, in some cases, distinguishing between the effects of iron on hemoglobin level versus cellular function.

Krayenbühl and colleagues take us a measured step further by demonstrating the improvement in fatigue symptoms in a group of nonanemic premenopausal women in a double-blind, placebo-controlled trial of intravenous iron.1 To qualify for the study, the subjects had to have fatigue as a major complaint, low iron stores (defined as serum ferritin ≤ 50 ng/mL), and to have a normal hemoglobin concentration. Intravenous iron, totaling 800 mg given in 4 doses over 2 weeks, led to an improvement in symptoms of fatigue as measured by the Brief Fatigue Index.7 The improvement was most marked and statistically significant in those women whose baseline serum ferritin was ≤ 15 ng/mL and the improvement, measured first at 6 weeks, was sustained over 12 weeks. Importantly, the hemoglobin levels did not change, indicating that it was the iron that led to the improvement in symptoms. A major strength of the study was the manner of blinding, which prevented any of the study subjects from seeing what was being infused and any of the investigators from knowing what the study subjects were getting. The mechanism of blinding and the route of administration of iron (designed to avoid the high gastrointestinal side effect profile of oral iron) were critical to being able to interpret the results of the study.
What is the likely mechanism behind the lessening of fatigue? Iron is necessary to maintain key enzymes in the mitochondrial electron transport system. Among these enzymes are several mitochondrial oxidases (see figure). These enzymes power muscle function through the generation of adenosine triphosphate (ATP), as shown. Iron has a strong redox potential and is built into the prosthetic groups of 3 major transmembrane enzymes in the inner mitochondrial membrane. The redox potential of iron allows quick alternation between the reduced ferrous (Fe\(^{2+}\)) state and an oxidized ferrous state (Fe\(^{3+}\)) during electron transport along the membrane, thus affording efficient shuttling of positively charged hydrogen ions (H\(^+\)) through the membrane. The proton gradient powers the synthesis and release of ATP, thus playing a critical role in energy production.

In classic experiments performed in the 1970s, Finch and colleagues unequivocally separated the effects of hemoglobin concentration from iron on exercise capacity in rats, using treadmill running time as the end point. With hemoglobin concentrations held equal at about 10 g/dL, iron-deficient rats had impaired running times compared with non–iron-deficient rats. With the administration of parenteral iron, exercise capacity normalized within 4 days in the deficient animals. Rates of oxidative phosphorylation with several substrates were reduced in the skeletal muscle of the iron–deficient rats.

The findings of Krayenbuhl et al are consistent with the findings in experimental animals. With this new information in hand, should every subject complaining of fatigue be given parenteral iron? Clearly, the answer is, “not yet,” but the current study, and the results of other recently published reports demonstrating benefit in muscle (cardiac) function in patients given parenteral iron, has to be taken seriously. The findings raise a number of important questions.

How much iron is necessary to see the effect and how should the iron be administered? The amount of iron given to the subjects in this study was large, and likely greatly exceeded that needed to replenish mitochondrial enzymes. And, while the subjective adverse event profile in this study was acceptable, if enough subjects are given parenteral iron, some serious events will occur. Thus, subject selection will need to be refined and studies comparing oral with parenteral iron would be helpful.

Can more objective measures of effectiveness, such as exercise capacity or cognition, be used in future studies? That might not be so easy, because it is likely that exercise capacity and cognition can both be affected adversely by the subject feeling “fatigued.”

Can the ferritin cut-off be refined? Entry into this study required a ferritin of \(\leq 50\) mg/mL but the major (and statistically significant) effect was seen in those women whose serum ferritin was \(\leq 15\) mg/mL. With larger numbers of subjects, a different cut-off might emerge, allowing benefit for greater numbers of patients.

Clearly, further studies of the potential beneficial effects of iron supplementation are warranted. The past 10 years have seen the introduction of several new and very safe parenteral iron products. The details of when and where to use these products need to be ironed out.

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REFERENCES


Lymphoid Neoplasia

Fox and Blimp in NK-cell lymphoma

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In this issue of Blood, Karube and colleagues have identified FOXO3 and PRDM1 (Blimp1) as tumor suppressor genes with a potentially critical role in the pathobiology of extranodal NK/T-cell lymphoma and aggressive NK-cell leukemia.

Extranodal NK/T-cell lymphoma, nasal type (ENTKL) and aggressive NK-cell leukemia (ANKL) are rare hematologic malignancies with an unfavorable prognosis and an increased prevalence in Asia and South America. Malignant cells are universally associated with the clonal episomal Epstein–Barr virus (EBV) form and frequently harbor numerous cytogenetic abnormalities. Wong et al identified a recurring deletion in the long arm of the chromosome 6q21q25 in NK-cell lymphoma/leukemia, suggesting that this region contains a putative tumor suppressor gene. Interestingly, deletions in the chromosome 6q21 have also been found in patients with solid tumors and B-cell lymphomas. The analysis of clinical samples and cell lines in diffuse large B-cell lymphoma (DLBCL) with del(6q21) identified mutations in several down-regulated candidate genes including PRDM1 (PR domain zinc finger protein 1), also known as Blimp-1 (B-lymphocyte-induced maturation protein). PRDM1 is a pleiotropic repressive transcription factor that is essential for the terminal differentiation of antibody-producing cells. For many years, it was believed that PRDM-1 is B cell–specific but more recent reports have suggested that it also plays a pivotal role in the regulation of NK-cell activation and maturation. Recently, several research teams have attempted to identify genes important in the pathogenesis of NK-cell lymphoma/leukemia. Although numerous chromosomal gains and losses were detected in nonanemic, premenopausal women with low serum ferritin concentration.

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