Iron Deficiency: Implications Before Anemia

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EDUCATION GAP

Clinicians should recognize iron deficiency as a unique disease entity and understand the interconnection between iron deficiency and other systemic diseases.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize that iron deficiency is a separate entity that precedes iron deficiency anemia and in and of itself causes serious morbidity.
2. Identify iron deficiency as an associated sign for multiple underlying diseases, including inflammatory bowel disease and hereditary hemorrhagic telangiectasia.
3. Discuss the vulnerability of the brain to iron depletion.
4. Describe options for replenishing iron stores and the improvements in parenteral formulations of iron.

INTRODUCTION

Iron plays a role in multiple essential physiological functions, including oxygen transport, gene regulation, DNA synthesis, DNA repair, and brain function. Depletion of and inability to use iron disrupts these pathways and causes multiple morbidities. Iron deficiency anemia (IDA) is a well-known sequela, but iron deficiency alone, before the manifestation of microcytosis and anemia, may have negative implications for the health of pediatric patients.

Of children 0 to 4 years of age, 20.1% have IDA in industrialized countries and the same is true of 39% of children in nonindustrialized countries. (1) Iron deficiency, independent of anemia, affects 2.3 billion people worldwide, including 50% of younger children and female teenagers. The recognition that iron deficiency puts children at risk for a myriad of poor outcomes is an important step in delivering effective health-care.

IRON HEMOSTASIS

Iron is absorbed from the diet in primarily the duodenum and the jejunum. The body has been known to regulate the amount of absorption; it has been estimated that a diet with 10 to 20 mg of iron leads to approximately 1 mg of iron absorption.

AUTHOR DISCLOSURE Drs Tong and Vichinsky have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Dietary iron can take various forms when consumed. Heme iron, the iron associated with meat intake, represents approximately one-third of the dietary iron but contributes to two-thirds of the body iron. Heme iron is preferentially absorbed because it is soluble at the pH of the intestine. In contrast, the most common dietary form of iron, ferric or Fe3+ iron, must be chelated in the acidic environment of the stomach and stay chelated until it is absorbed via the β_3 integrin and mobilferrin pathway; without this chelation step, iron is insoluble in the intestine due to the small intestine's comparatively more alkalotic pH and cannot be absorbed. Ferrous or Fe2+ iron is the reduced form of ferric iron and is absorbed through a different pathway than the forms noted previously herein. Vitamin C (ascorbic acid) facilitates the reduction of ferric iron. Non-heme iron sources are, therefore, more difficult for the human body to absorb (can become insoluble, require chelation) compared with heme iron (soluble in the normal duodenal pH). (2)

Recent research elucidated one of the key players in the regulatory process, hepcidin, which is now considered the central regulator of iron, affecting how the gastrointestinal tract, liver, and macrophages contribute to iron homeostasis. Hepcidin regulates the activity of the iron exporter, ferroportin, located on the basolateral membrane of enterocytes, hepatocytes, and macrophages. The binding of hepcidin to ferroportin leads to the internalization of ferroportin, reducing the amount of iron available in the plasma. (3) High levels of hepcidin, therefore, lead to sequestration of iron, reducing the amount available for functions such as erythropoiesis and DNA synthesis.

Factors that influence the release of iron from the liver include intracellular and extracellular levels of iron, inflammation, and erythropoietic iron demands. High levels of iron and inflammation upregulate hepcidin production, whereas an erythropoietic signal downregulates hepcidin to make more iron available to bone marrow.

In cells, iron is processed as either transferrin-bound iron or non–transferrin-bound iron, both of which contribute to the labile iron pool. Ferritin is a major intracellular storage protein for iron, but if the pool of iron is too large, another pathway becomes available; free iron produces free radicals. This oxidative stress can damage organelles and impair cellular function.

IRON DEFICIENCY: CLINICAL CLASSIFICATION

Deficits in iron can be divided into 4 major categories: 1) Iron depletion describes a state in which the low level of iron affects nonhematologic pathways (brain, muscle); as such, one does not see the microcytic anemia that is classically seen in IDA. 2) Iron-restricted erythropoiesis applies to a state in which there is some impairment of hematologic function without evidence of anemia or microcytosis. 3) IDA represents the clinical picture with a decreased hemoglobin level, (4) at which point neurodevelopmental and musculoskeletal functions have already been hindered. 4) Functional iron deficiency defines a state in which iron stores are adequate but unavailable for biological use. The typical laboratory findings of each category can be seen in Table 1.

The epidemiology of true iron deficiency is hard to determine, but using anemia as a rough surrogate, the burden of disease is large. The 2001 World Health Organization report used an estimate of 30% to 40% of those with iron deficiency to manifest as cases of IDA. Iron deficiency is, therefore, thought to affect more than 2 billion people worldwide; the distribution varies according to age, sex, geography, and socioeconomic status, but in nonindustrialized countries, approximately 50% of children and teenaged girls have IDA. (1)

IRON DEFICIENCY: THE CONSEQUENCES

Iron deficiency affects a variety of physiological functions. Iron deficiency alone has been associated with long-lasting consequences on neurodevelopmental outcomes; standard test scores of 11- to 14-year-olds who had iron deficiency as infants demonstrate worse performance on 6 different tests, including the Full-Scale IQ and the Wide Range Achievement Test Arithmetic and Reading. (5) A group of infants was followed to 25 years of age, and the study demonstrated increased odds of failure to complete secondary school and of having neuropsychiatric deficits, including negative emotions, detachment, and poor self-rating of emotional health, compared with iron-sufficient control subjects. (6) Trying to isolate the effect of iron status in these studies is understandably difficult, and changes could be related to an unidentified confounder, but the associations are worth acknowledging with the potential of iron deficiency to affect individuals throughout their whole life. An iron-deficient state has further been linked to attention-deficit/hyperactivity disorder (ADHD) and restless legs syndrome (RLS). Visual and auditory deficits can also be seen. Physiologically, these changes may be mediated by neuronal hypomyelination and decreased neurotransmitter function. (7) In addition, in rats that model neonatal dendritic sprouting in the setting of iron deficiency, as simulated with deferoxamine chelation, investigators demonstrated shortening of the morphology of neuronal branches and a reduction in the number of primary dendrites in the hippocampus. (8) These sets of changes in the brain may underlie the impairments

Table 1. Classification of Iron States and Associated Laboratory Findings

LABORATORY FINDING	IRON DEPLETION	IRON-RESTRICTED ERYTHROPOIESIS	IRON DEFICIENCY ANEMIA	FUNCTIONAL IRON DEFICIENCY
Hemoglobin concentration	Normal	Normal	Reduced	Normal
Mean corpuscular volume	Normal	Normal to reduced	Reduced	Reduced
Serum iron concentration	Normal	Reduced	Reduced	Normal
Serum ferritin concentration	Reduced	Reduced	Reduced	Normal to elevated
Total iron binding capacity	Normal	Increased	Increased	Increased
Soluble transferrin receptor	Normal	Increased	Increased	Increased
Reticulocyte hemoglobin content	Normal	Decreased	Decreased	Decreased
Hepcidin	Reduced	Reduced	Reduced	Elevated

of neurodevelopment in children with iron deficiency and may contribute to the observed long-lasting negative impact of this micronutrient deficiency.

Immune system function has also been linked to low iron levels and can lead to decreased levels of the cytokine interleukin-6, diminished phagocytic activity, and impaired oxidative burst activity. (9) Impaired muscle metabolism due to decreased oxygen diffusion and reduced mitochondrial oxidative capacity is another manifestation. (10) Gastric atrophy, achlorhydria, chronic duodenitis, and villous atrophy have been seen in pediatric patients with IDA. (11)(12) In anemic women, compared with controls, an impaired response to cold stimulus has been observed; at baseline and after the cold stimulus, the group of anemic women had lower levels of thyroxine and triiodothyronine as well. The authors stipulate that this effect is mediated by decreased thyroid peroxidase in the setting of iron deficiency. (13)(14) Iron deficiency can contribute to chronic fatigue, especially in premenopausal women. This fatigue seems to respond to iron replenishment; in a group of nonanemic women with poor iron status (ferritin level 15 ng/mL [15 μg/L]), iron improved their fatigue score. (15)

EVALUATION OF IRON DEFICIENCY

There are multiple different tests that have been used to evaluate iron deficiency, including hemoglobin concentration, mean corpuscular volume (MCV), reticulocyte hemoglobin content, serum iron concentration, serum ferritin level, total iron binding capacity, soluble transferrin receptor, protoporphyrin level, and red blood cell distribution width (RDW). (16) Of these, ferritin concentration is the only one to be decreased in the setting of iron depletion without anemia, whereas changes from the normal range can routinely be seen in all of these parameters once IDA can be appreciated. Of note, though, the traditional ferritin cutoff value of 12 ng/mL (12 μg/L) has been shown to have 25% sensitivity, whereas a level of 30 ng/mL (30 μg/L) has improved sensitivity of 93% using bone marrow iron status as the "true" indicator of iron status. (17) In iron-restricted erythropoiesis, hemoglobin concentration and MCV can be normal, but the other parameters are typically affected.

Microcytic anemia can present in both IDA and anemia of chronic disease (ACD); in these cases, inflammatory markers prove useful in the differentiation of these entities. In ACD, cytokine, hepcidin, and ferritin levels tend to be elevated, with increased bone marrow iron content of macrophages. The soluble transferrin receptor level is usually normal in ACD. Nevertheless, both entities, ACD and IDA, present with decreased plasma iron.

The oral iron challenge can help differentiate patients who are iron deficient. After a dose of oral iron, peak serum iron levels are higher in those with iron deficiency compared with those who are iron sufficient. In patients with inflammatory bowel disease, the absorption of iron is less in patients with active disease than in those with inactive disease. The inflammatory milieu decreases iron absorption, which reinforces the importance of differentiating IDA and ACD due to differential response to therapeutic intervention. (18)

In pediatrics, risk assessment with a particular focus on diet history for iron deficiency is performed at 4, 15, 18, 24, and 30 months, and then annually. Laboratory tests are routinely performed at 9 to 12 months, 18 months in high-risk infants, during a growth spurt, and during menses (13–17 years old). Screening intervals are adjusted for high-risk individuals, athletes, vegans, patients with menorrhagia, patients with chronic disease, and obese patients. (19)(20) The screening laboratory tests that are recommended by the American Academy of Pediatrics are complete blood cell

(CBC) count, reticulocyte count, MCV, RDW, ferritin level, C-reactive protein level, and reticulocyte hemoglobin concentration (CHr). (19) CHr represents a newer test that is thought to be an early indicator of iron deficiency before anemia, and it outperforms MCV and ferritin as an early indicator when cases of MCV greater than 100 fL are excluded. (21) The CHr value tends to increase within 2 to 3 days of starting iron therapy. Normal values of CHr are typically greater than 28 pg. (16) Historically, the gold standard diagnostic test for IDA is the therapeutic trial of iron, in which patients are reevaluated 1 month after starting oral iron to look for a change in the CBC count parameters.

CAUSES OF IRON DEFICIENCY

Iron deficiency is the most common nutritional deficiency in the world. Interestingly, the IDA prevalence fell from 1990 to 2010, but in the subgroup of children younger than 5 years, the prevalence rose. (22) The steps that lead up to this can be numerous but stem primarily from diet. Single-food diets of infancy, in particular unfortified cow milk, nutritionally inadequate diet, and consumption of foods that interfere with iron absorption (tea, bran, fiber, antacids, phosphates, calcium) can all play a role.

Adequate iron intake for a newborn until 6 months of age is 0.27 mg daily, which is a calculated value. Stores of iron for full-term infants are sufficient until age 4 months, at which point it is suggested that exclusively breastfed infants have iron supplementation of 1 mg/kg per day until their diet includes more iron-rich sources. From 7 to 12 months, the daily recommendation is 11 mg, and from 1 to 3 years of age, 7 mg is suggested. (19) Nutritional requirements change with developmental requirements, dictating the need for higher dietary iron. These situations include prematurity, intrauterine growth restriction, infants of diabetic mothers, age 13 to 17 years, patients breastfed after 4 months of age, menstruation, and pregnancy. For example, premature babies have a goal of 2 mg/kg per day of iron intake until 1 year of age.

Iron deficiency has a wide range of causes (Table 2). Iron can be lost through the gastrointestinal system, genitourinary system (menorrhagia, hemosiderinuria), and pulmonary system (pulmonary hemosiderosis).

Impairment of iron absorption represents another etiology of iron deficiency. Subclinical celiac disease represented approximately 30% of 2,000 total cases of celiac disease diagnosed in children in 1990 to 1994 in Italy; the most common manifestation was iron malabsorption, as indicated by IDA. This was seen in 34.3% of the pediatric patients, with short stature representing the second most common sign at 29%. (23) *Helicobacter pylori,* one of the most prevalent chronic bacterial infections worldwide, oftentimes presents asymptomatically in children but can cause IDA. *H pylori* infection was more prevalent in children with IDA (31.3%) versus children without IDA (15.5%) in a study that examined the relationship between infection, iron deficiency, and short stature. (24) Infection with *H pylori* has been shown to cause gastritis and modify gastric ascorbic acid content; these factors contribute to the decreased gastric absorption due to the importance of low gastric pH in chelation of ferric iron and the role of ascorbic acid in reduction of ferric iron. (25) Initially, as many as 75% of patients with *H pylori*–associated IDA will not respond to oral iron, but *H pylori* treatment can improve the response; some studies have even demonstrated resolution of IDA without supplementation of iron. (26) Autoimmune gastritis and inflammatory bowel disease can also lead to insufficient iron stores.

Iron-resistant IDA is due to an autosomal recessive mutation in the *TMPRSS6* gene, which codes for a transmembrane serine protease that downregulates the BMP-SMAD signaling cascade known to have hepcidin as an end product. (27) Mutations, therefore, prevent the appropriate downregulation of hepcidin, resulting in failure of iron absorption even in iron-deficient states. Patients with iron-resistant IDA do not respond to oral iron and have a partial response to parenteral iron.

Localized cellular deficits in iron uptake or mitochondrial utilization of iron can also cause iron deficiency and have been noted in patients with RLS.

Dietary iron represents only a part of the story for developing iron deficiency, and the complex interplay between iron homeostasis and multisystem disorders underscores the importance of iron in many physiological processes.

PARTICULAR POPULATIONS AND BLEEDING

Certain patient populations are at increased risk for iron deficiency. Preterm infants are at increased risk due to the timing of iron accumulation in the fetus; 80% of iron stores are acquired during the third trimester of pregnancy, and preterm infants miss out on this critical time to build iron stores. (19) Looking at a cohort of mothers who did or did not have IDA in China, investigators demonstrated decreased mental development of infants at 12, 18, and 24 months of age as assessed on a mental development index in the IDA group. Mothers were also randomized to replenishment with folic acid/iron, folic acid, or macronutrient, and a subgroup analysis demonstrated reduction of the difference in mental

Table 2. Etiologies of Iron Deficiency

CAUSE	EXAMPLES
Inadequate dietary iron intake	Single-food diet in infancy, unfortified cow milk >20 oz
	Diet, fasting, malnutrition (iron is better absorbed from meat versus vegetables (30% versus 10%)
	Diet containing inhibitors of iron absorption: tea, bran, fiber, phosphates, calcium, antacids
Developmentally required increased iron requirements	Premature, intrauterine growth restriction, infant of diabetic mother
	Newborns breastfed after 4 mo
	Children aged 13–17 y
	Menstruation
	Pregnancy
Increased acquired iron requirements	Overweight/obese adolescents
	Adolescent athletes
Increased iron losses	Menorrhagia
	Gastrointestinal/genitourinary bleeding
	Hemosiderinuria from intravascular hemolysis
	Parasitic infections
	Exercise-related
	Pulmonary hemosiderosis
Decreased iron absorption	Celiac disease, inflammatory bowel disease
	Autoimmune atrophic gastritis
	Helicobacter pylori infection
	Iron-resistant iron deficiency anemia (hereditary)
	Chronic inflammation
Localized cellular mutations alter Fe iron uptake or mitochondrial transport	Restless legs syndrome

development index in the infants of mothers who had iron and folic acid supplementation but not in the infants of mothers who took only folic acid or macronutrient. (28) There has been much attention to the idea of delayed cord clamping as a means of providing more placental blood and iron to the neonate. A systematic review concluded that delayed cord clamping of greater than 2 minutes leads to elevated ferritin levels in the infant up to 6 months of age compared with early cord clamping (5–10 seconds). (29) A recent trial demonstrated effects up until 12 months of age with delayed cord clamping of greater than 3 minutes compared with an "extended" cord clamping (<60 seconds). At 8 months, delayed cord clamping was associated with higher ferritin levels and decreased risk of iron deficiency and IDA. At 12 months, delayed cord clamping was associated with decreased risk of IDA only. (30)

Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia) is an autosomal dominant condition that has a prevalence between 1 in 5,000 and 1 in 8,000, and it is much more common in the Afro-Caribbean population. Clinical manifestations include epistaxis, mucosal telangiectasias, and malformations of various organ systems, including pulmonary and gastrointestinal. Nosebleeds are more commonly the presenting symptom in children versus adults with this disease; in pediatrics, 90% of patients present initially with epistaxis, and the clinical finding of telangiectasia can lag from 5 to 20 years afterward. (31) These patients can present with epistaxis and IDA without other symptoms. This iron deficiency is an important risk factor for stroke in patients with pulmonary arteriovenous malformations and is associated with changes in platelet aggregation responses. (32)(33) Identification and

diagnosis of these patients can help initiation of preventive therapy.

Adolescent girls are thought to be at risk for IDA, especially those with menorrhagia. The objective definition of greater than 80 mL per cycle of blood loss is often difficult to apply in practice, but multiple visual scales can be used to estimate blood loss, including the pictorial blood loss assessment chart and the menstrual pictogram. (34) Other indicators include soaking of a pad in less than 2 hours, bleeding into clothes, or blood clots larger than 1 inch.

Athletes are another at-risk group; possible mechanisms are blood losses due to microscopic lesions in the gastrointestinal/genitourinary systems secondary to changes in circulation during exercise and sequestration of iron in the setting of inflammation-induced increases in hepcidin. (35) Rowland et al (36) followed high school runners through a season and found that the proportion of iron deficiency in both male and female runners increased. A meta-analysis looking at the effects of iron repletion linked improvement in exercise performance as measured by oxygen consumption. (37) Randomized double-blinded studies among female recruits to the army also demonstrated a beneficial effect in patients with IDA in terms of mood and exercise performance; it is notable that their study demonstrated no difference in recruits who had iron deficiency, which was defined as abnormalities in 2 of the 3 parameters of RDW, ferritin level, or transferrin saturation. (38) The International Olympic Committee has recommended a CBC count for all female athletes and a hemoglobin and ferritin screen for all endurance sport athletes. (39)

Obesity has also been linked to IDA in teenagers; both overweight and obese teenagers had an odds ratio of 2:1 for having iron deficiency (defined as 2 of 3 abnormal laboratory values) compared with patients with a BMI less than 85% with a prevalence of 3.5%, 7.2%, and 9.1% for normal BMI, overweight, and obese teenagers, respectively. (40) In Israel, the prevalence of iron deficiency, defined as a serum iron level less than 45 μg/dL (<8.05 μmol/L) in their study, in normal, overweight, and obese children was 4.4%, 12.1%, and 38.8%, respectively. (41) In 2012, the rate of obesity in children 6 to 11 years of age was 18% and in 12- to 19-year-olds was 21%. (42)(43) This is a significant portion of the youth who are at risk for iron deficiency and the associated biopsychological outcomes.

IRON HOMEOSTASIS IN NEUROLOGIC DISORDERS

Iron deficiency has been linked to ADHD and RLS; a possible link has been seen in animal models, in which a state of iron deficiency led to changes in dopamine receptor expression. ADHD and RLS have also been noted to be comorbid; of patients with ADHD, 44% had RLS symptoms, and of patients with RLS, 26% had ADHD symptoms. RLS has a prevalence of approximately 5% in pediatric patients, and most of these children have a family history. (44) Symptoms include sleep disturbances, restlessness, and inability to control limb movements. Intravenous iron therapy with low-molecular-weight dextran has demonstrated improvement in patients with iron deficiency and RLS. In a sample of 42 patients, 32 (76%) had subjective improvement of symptoms after a single infusion of iron dextran; 20 of 42 patients (48%) had improvement of symptoms lasting longer than 6 months. (45) There has been some debate as to the correlation of brain iron to peripheral iron; iron dextran, iron isomaltoside, or ferric carboxymaltose, with their higher incorporation into macrophages, may allow for greater iron delivery to the brain. (46) The overall mechanistic link is not straightforward because there seems to be a change in the way patients with RLS regulate brain iron, which implies that higher doses of intravenous iron may be required for symptomatic improvement. (46)

ADHD affects approximately 11% of children. (47) Recently, Adisetiyo et al (48) evaluated iron levels with a magnetic field correlation metric in patients with ADHD not taking medications, patients with ADHD, and control patients. The data demonstrate decreased iron levels in the putamen, caudate, and thalamus in patients with ADHD not taking psychostimulant medications compared with control patients and patients with ADHD taking psychostimulant medications. (48) A small study of 23 nonanemic children with ferritin levels less than 30 ng/mL (<30 μg/L) with ADHD demonstrated improvement on the Clinical Global Impression–Severity scale after 12 weeks of oral iron therapy compared with placebo. (49) Although the studies were small, there is evidence that addressing iron deficiency in RLS and ADHD provides symptomatic benefit.

MANAGEMENT

Dietary interventions to improve iron intake are also worth discussing. Foods rich in iron typically include flesh foods (animal products such as red meats and pork), legumes (beans, lentils), dried fruits (prunes, raisin, apricots), and iron-fortified cereals. Reducing consumption of beverages such as coffee or tea that can affect iron absorption can be recommended. In infants, we advise limiting daily cow milk consumption to less than 24 oz. A fairly small study evaluated the effect of dietary intervention versus oral iron versus placebo on the iron status of nonanemic women; they

demonstrated improvement of ferritin levels at 16 weeks of intervention in both the dietary intervention and oral iron groups. The authors, however, state that dietary intervention may not be the most practical approach to mild iron deficiency in the general public. The study provided an "intensive and expert individualized dietary program," and even with that support, the patients "achieved only a small increase in their intake of flesh foods." The authors also note that the serum ferritin level increased to a greater extent in the oral iron supplementation group. (50) Diet should, nevertheless, be incorporated into the management of those with iron deficiency.

Oral iron preparations are widely used in therapeutic trials for IDA. A recent Cochrane review suggested that iron supplementation for menstruating females reduces the risk of iron deficiency and anemia, reduces fatigue, and improves exercise performance. Iron supplementation demonstrated gastrointestinal adverse effects, but low doses (<30 mg of elemental iron daily) can provide benefit and reduce the risk of adverse effects. (51) Moretti et al (52) also evaluated iron absorption in iron-deficient women older than 18 years using dosing schedules of once a day or twice a day; they found that iron absorption decreased and hepcidin levels increased with daily dosing. Moretti et al plan to query alternate-day iron dosing given their findings. Longer-term follow-up of their dosing schedules is lacking. (52) The recommendations for iron supplementation in pediatrics is typically 3 to 6 mg/kg per day of elemental iron given on a schedule from daily to 4 times a day. Typically, patients treated for IDA return to the clinic 4 to 8 weeks later for a repeated hemoglobin measurement. Treatment courses should last for at least 3 months, and even after discontinuation of iron therapy it is reasonable to review and encourage consumption of iron-rich foods. There are multiple different iron preparations, with ferrous salts (ferrous sulfate, ferrous gluconate, ferrous fumarate) being the most common. As many are aware, compliance is a challenge with oral iron; polysaccharide complex was a product that was thought to be more palatable, but a study in 80 nutritionally iron-deficient anemic children demonstrated greater improvement in hemoglobin levels for patients taking ferrous sulfate versus polysaccharide complex. (53) Multiple intravenous preparations are also available and are safe and effective. Originally, the high-molecular-weight iron dextran was used and had many adverse effects, in particular, anaphylaxis. The next generation of parenteral irons, which includes low-molecular-weight dextran, ferric gluconate, and iron sucrose, all have favorable adverse effect profiles; adverse effects can be seen in approximately 1% of patients, with only 1 in 200,000 having a severe adverse effect. Nevertheless, patients, especially those with multiple drug allergies, should be monitored for symptoms of anaphylaxis. New third-generation forms (ferumoxytol, ferric carboxymaltose) are also now available. Iron sucrose remains the most commonly used. (54)

Iron should be given with caution when iron status is not known. Majumdar et al (55) looked at the impact of oral iron on weight gain and linear growth in iron-deficient and iron-replete individuals. Iron was of benefit to the iron-deficient group, but iron therapy was correlated with decreased weight gain and linear growth in the iron-replete group. Lozoff et al (56) also looked at iron-fortified versus iron-low formulas in children and found that those with higher pretreatment hemoglobin levels receiving iron-fortified formula had worse neuropsychiatric testing results at 10-year follow-up compared with those with similar hemoglobin levels who had low iron content formula. Among patients with pretreatment hemoglobin levels less than 10.5 g/dL (<105 g/L), those who had iron-fortified formula had improved testing at the follow-up point. (56) Iron therapy is safe, and the newer parenteral formulations have rare adverse effects; similar to any medication though, it must be used in the correct clinical context.

CONCLUSIONS

Iron deficiency without IDA may impact development and physiological function. Dietary iron deficiency represents a significant global burden, and there are many children who are unscreened and untreated. Early treatment may prevent the negative outcomes associated with iron deficiency and relieve associated symptoms, but more trials are needed to determine the true benefit. Iron deficiency may represent a feature of underlying systemic illness, and in the context of appropriate history, it could alert clinicians to consider these possible etiologies in patients belonging to high-risk populations. IDA is only part of a much larger health-care problem, and once IDA appears, many physiological functions have already been impaired.

Summary

- Based on research studies, evidence quality C, iron deficiency without changes in hematologic parameters could have substantial implications for the health of children, in particular, their neurocognitive development.

- Based on research studies, evidence quality D, iron deficiency can be due to nutritional factors but can also represent a manifestation of a systemic illness such as hereditary hemorrhagic telangiectasia or celiac disease.
- Based on research studies and recent Cochrane reviews, evidence quality B, low-dose iron supplementation is appropriate for menstruating females.
- Based on research studies, evidence quality D, there are many children at risk for iron depletion who go unrecognized and unscreened.
- Based on research studies, evidence quality C, parenteral iron is safe and indicated in several conditions.

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 1/11.

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1. A 3-year-old boy presents with poor weight gain. He has a normal hemoglobin level and mean corpuscular volume (MCV), with elevated total iron binding capacity and a decreased ferritin level. Which of the following is most consistent with the pathophysiology of his clinical presentation and laboratory findings?

   A. Anemia of chronic disease.
   B. Functional iron deficiency.
   C. Iron deficiency anemia.
   D. Iron depletion.
   E. Iron-restricted erythropoiesis.

2. A 1-year-old boy diagnosed as having iron deficiency anemia is brought to the clinic for follow-up. His mother is worried about any long-lasting consequences if the anemia is not corrected in a timely manner. In discussing with the mother what is known about this topic, which of the following conditions has been associated with iron deficiency?

   A. Attention-deficit/hyperactivity disorder.
   B. Diabetes mellitus.
   C. Hyperthyroidism.
   D. Liver dysfunction.
   E. Rheumatoid arthritis.

3. A 17-year-old girl with menorrhagia is found to have a hemoglobin level of 8.7 g/dL (87 g/L), MCV of 62 fL, and ferritin level of 2 ng/mL (2 μg/L). She is started on oral iron supplementation. Which of the following is the earliest indicator of response to iron therapy?

   A. MCV.
   B. Red blood cell distribution width.
   C. Reticulocyte hemoglobin concentration.
   D. Serum ferritin.
   E. Total iron binding capacity.

4. A 10-year-old girl presents with pallor and frequent epistaxis and is found to have microcytic anemia. On physical examination, she has small dilated blood vessels in the oral mucosa. Which of the following is the most likely diagnosis in this patient?

   A. Celiac disease.
   B. Hereditary hemorrhagic telangiectasia.
   C. Hemosiderosis.
   D. Hypothyroidism.
   E. Iron-resistant iron deficiency anemia.

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5. A 2-year-old girl presents with pallor and is found to have a hemoglobin level of 6.8 g/dL (68 g/L) and an MCV of 55 fL. She drinks 40 oz of cow milk per day. Her activity level is normal, and her vital signs are stable. In addition to dietary counseling, which of the following is the most appropriate management plan for this patient?

   A. Give ferrous sulfate for at least 3 months.
   B. Give iron polysaccharide complex until the hemoglobin level normalizes.
   C. Replace cow milk with iron-fortified formula.
   D. Start on iron-rich food and repeat complete blood cell count in 1 month.
   E. Transfuse with packed red blood cells.

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Pediatrics in Review 2021;42;11
DOI: 10.1542/pir.2018-0134

Pediatrics in Review®
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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