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REVIEW
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Iron Deficiency Anemia in Infancy, Childhood, and Adolescence

Tekin Aksu, Şule Ünal

Department of Pediatric Hematology, Hacettepe University, Ankara, Turkey

ABSTRACT

Iron deficiency is the most common nutrient deficiency in the world. Epidemiological data indicate that iron deficiency is more prevalent in infants, in preschool-children, and in adolescents. Etiologies of iron deficiency in children include inadequate dietary iron intake, which is the most common cause, as well as increased iron requirements, bleeding, and intestinal iron absorption disorders. Iron deficiency can lead to symptoms related to anemia, may interfere with neurodevelopment and may cause skin, hair, nail, and gastrointestinal problems. This review focuses on the causes, signs, symptoms, diagnosis and management of iron deficiency in infancy, childhood, and adolescence.

Keywords: Iron deficiency, anemia, children

INTRODUCTION

Iron deficiency is the most common nutrient deficiency in the world and is a public health problem. According to the World Health Organization (WHO) report in 2008, 24.8% of the world's population is anemic, and iron deficiency (ID) is the cause of anemia in half of the cases.[1] In developing countries, about 40%–50% of children under 5 years suffer from ID. The incidence of ID in children and adolescents in Turkey has been reported in various publications, ranging from 6.5% to 42% in different regions.[2,3]

Iron deficiency is defined as a lack of iron in the body that does not prevent the production of hemoglobin, and ID anemia is defined as a decrease in the amount of hemoglobin due to ID. A positive iron balance is achieved in childhood with about 1 mg of iron intake per day. Since about 10% of dietary iron is absorbed, 8–10 mg of dietary iron should be consumed daily. Iron deficiency is most common in infancy and early childhood and second most common in adolescence. Anemia is described as a decrease in hemoglobin, hematocrit, or red blood cell count. A hemoglobin value that differs by more than 2 standard values from that of children of the same age and gender is considered as anemia (Table 1).[4,5] While a hemoglobin value below 11 g/dL in children 6–59 months of age is considered as anemia, 11.5 g/dL in children 5–11 years of age, 12 g/dL in children 12–14 years of age and for women above 15 years of age, and 13 g/dL in men above 15 years of age can be accepted as lower limits for anemia.[6]

CAUSES OF IRON DEFICIENCY

Causes of ID in children include inadequate dietary iron intake, which is the most common cause, as well as increased iron requirements, bleeding, and intestinal iron absorption disorders.[7] Iron is present in small amounts in both breast milk and cow's milk, but about 50% of the iron in breast milk is absorbed, whereas only 10% of the iron in cow's milk is absorbed. Excessive consumption of cow's milk leads to decreased absorption of other nutrients and iron-containing medications. Use of cow's milk during the initial year of life may also lead to ID anemia (IDA) through gastrointestinal occult/overt blood loss due to cow's milk protein-induced colitis.[8] Iron stores are sufficient for the first 6–9 months of life in term infants.

Corresponding author:
Şule Ünal
✉ suleunal@hacettepe.edu.tr
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Table 1. Means and −2 SDs of Hb and MCV Values by Age

	Hemoglobin (g/dL)		MCV (fL)	
Age	**Mean**	**-2SD**	**Mean**	**-2SD**
1 month	14	10	104	85
2 months	11.5	9	96	77
3-6 months	11.5	9.5	91	74
0.5-2 years	12	10.5	78	70
2-6 years	12.5	11.5	81	75
6-12 years	13.5	11.5	86	77
12-18 years (female)	14	12	90	78
12-18 years (male)	14.5	13	88	78

Modified from Dallman.[5]
MCV, mean corpuscular volume.

However, infants with preterm birth, low birth weight, or perinatal blood loss have inadequate iron stores and may develop IDA in the first 2-3 months of life. Additionally, delayed cord clamping (1-3 minutes) decreases the risk of ID, whereas early cord clamping less than 30 seconds increases the risk of ID.[9] In cases where breast milk cannot be given, infants should receive iron-fortified formula for the first 9 months. After 6 months, it is recommended to give iron-rich complementary foods in addition to breast milk. From the first year of life, daily cow's milk consumption should be limited to a maximum of 500 mL.[10] Iron can be absorbed through the diet in the form of heme iron, which is found in excess in red meat and liver, or in the form of non-heme iron, which is found in other foods.[11] Because absorption of heme iron is not affected by gastric acid and occurs through a separate transport system, the absorption rate is up to 30%, while absorption of non-heme iron is 5%-10%. The risk of ID increases in people who receive a vegan diet or consume less meat because of socioeconomic reasons.[12] Factors that increase iron absorption should be included in the diet such as vitamin C, and attention should be paid to factors that decrease absorption. Milk and dairy products as well as phytates, tea, and coffee should not be taken with meals because they reduce the absorption of iron.

In infancy, especially between 9 and 24 months of age, the risk of ID increases due to the increased need for iron because of rapid growth and the inability to meet this need with complementary foods. Iron deficiency anemia is commonly observed in children who choose food are fed cow's milk, have a history of pica, and will not eat meat, vegetables, and iron-rich foods.[13] The prevalence of ID in school-aged children is lower than in other age groups. Iron deficiency anemia may result from causes that lead to blood loss, such as epistaxis and gastrointestinal losses (Meckel's diverticulum, hemangioma, and inflammatory bowel disease). In adolescent girls, the most common cause of ID is menstrual bleeding.[14] During puberty, ID may be encountered in both boys and girls due to rapid growth. Intestinal parasites are an important cause of ID, especially in endemic areas. Factors that reduce gastric acidity, including H2 receptor blockers, proton pump inhibitors, antacids, and surgical procedures such as gastrectomy, reduce iron absorption. Like celiac disease, malabsorption syndromes may also impair iron absorption, resulting in ID. In addition, epidemiological studies show that *Helicobacter pylori* infection of the gastric mucosa can lead to ID or IDA in children and adolescents. Recent studies suggest that *H. pylori* infection causes ID by affecting the bioavailability of iron, rather than by decreasing gastric acid secretion or causing significant bleeding in children.[15]

SIGNS AND SYMPTOMS OF IRON DEFICIENCY

Iron deficiency anemia in children is usually discovered during a complete blood count performed for some other reason without obvious symptoms. Pallor is the most common finding and may not be noticed until the hemoglobin drops below 7-8 g/dL. Pallor is best noticed on the palms, nail beds, and conjunctiva. Other symptoms and clinical signs of anemia are palpitations, dyspnea on exertion, headaches, tinnitus, vertigo, and syncope. Older children and adolescents may experience fatigue, chills, decreased cognitive function, and dizziness. If hemoglobin levels are too low, there may be loss of appetite, restlessness, lethargy, tachycardia, and heart failure.[14] Pica, i.e., eating non-nutritive materials (such as paper, soil, and ice), maybe the first clinical sign of ID.

Infants may present with complaints of breath-holding spells and disturbances in sleep patterns, developmental delay, or even regressions. These findings may be observed in the early stages of ID, even before anemia occurs. Iron deficiency in the first months of life may interfere with neurodevelopment such as myelination and neurotransmission. There are reports that the cognitive effects of IDA, which develop in infancy, can last a lifetime.[14] On the other hand, inability to concentrate, attention-deficit hyperactivity disorder, irritability, decrease in academic success, difficulty in understanding and perception, restless legs syndrome, and increased frequency of infections may occur due to functions of iron other than erythrocytes. The age of onset, duration, and severity of the ID may influence cognitive and neurophysiological outcomes in childhood.[16,17]

The patient may have decreased tongue papillae, burning tongue, decreased sense of taste, easy breakage of hair and nails, wrinkling of the nails, and angular cheilitis in the corners of the mouth. In rare cases, symptoms may also include spoon nails, blue sclera, and dysphagia, which are part of Plummer–Vinson syndrome.[18]

Iron also has immunological functions involving both innate and acquired immunity. It has been reported that in ID, the production of interleukin-2 (IL-2) and IL-6 is impaired, and the functions of leukocytes and lymphocytes are mildly to moderately impaired. In addition, nuclear factor kappa B is activated in the presence of intracellular iron. Nuclear factor kappa B is a transcription factor involved in the expression of some genes with immunological and inflammatory functions. For these reasons, infections may occur frequently in children with ID. On the other hand, there are data that iron supplementation may increase the risk of reactivation of some infections such as malaria or tuberculosis.[19]

Iron deficiency anemia has also been reported to be associated with an increased risk of cerebral venous thrombosis. Previously healthy children with stroke had a 10-fold higher risk of ID anemia than healthy children without stroke, and this may be related to the thrombocytosis that can accompany

Table 2. The Non-hematological Findings of Iron Deficiency	
General	Growth Delay
Neurological	Restlessness Decreased mental and motor functions Decreased mathematical processing and memory skills Decreased production of neurotransmitters Sleep disturbances Breath-holding spells Restless legs syndrome
Gastrointestinal	Anorexia Damage to epithelial tissue (glossitis, angular cheilitis) Esophageal web or stricture, gastric atrophy Damage of microvilli, enteropathy Pica
Skin	Koilonychia/spoon nails Easy breakage of nails and hair, hair loss

IDA.[20] The non-hematological findings of ID are summarized in Table 2.

LABORATORY FINDINGS OF IRON DEFICIENCY

In practice, the mean red cell volume (MCV) value is calculated according to the formula "70 fL+ age (years)" in 1-10 years of life. If the patient's MCV value is lower than the value calculated by this formula, it is considered as microcytosis. After the age of 10 and in adults, a value of less than 80 fL is considered as microcytosis. The association of elevated red cell distribution width (RDW) and low MCV are laboratory parameters that indicate ID. Hypochromia, microcytosis, anisocytosis, and poikilocytosis (elliptocytes and pencil cells) are observed in the peripheral blood smear.[21] Basophilic punctuation may be seen. Platelet count may be normal or increased and is rarely decreased in severe ID. Reticulocyte count is often normal, but there is no adequate reticulocyte response to anemia. Iron deficiency anemia is the last stage of iron deficiency and complete blood count is impaired only in patients at this stage.

Iron deficiency is reflected in a decrease in serum ferritin, which indicates iron stores in the body. A ferritin level below 12 ng/mL (mcg/L) in children under 5 years of age and below 15 ng/mL in children over 5 years of age is indicative of ID.[22] In the presence of infection or inflammation, the ferritin value cannot be considered reliable for diagnosing ID. Therefore, it is recommended that the value be interpreted along with C-reactive protein (CRP) and/or erythrocyte sedimentation rate. When there is a negative iron balance, serum iron (SD) decreases, iron-binding capacity (TIBC) increases, and transferrin saturation decreases. Transferrin saturation below 15% is indicative of ID. Serum iron and TIBC should be tested in the morning on an empty stomach. When there is no iron left to bind to protoporphyrin for heme production, free erythrocyte protoporphyrin (FEP) accumulates and hemoglobin synthesis is impaired. Free erythrocyte protoporphyrin is a very reliable test and is generally used for research purposes. As a result, a low hemoglobin level in the blood count, a decrease in MCV and mean red cell hemoglobin (MCH), and an increase in RDW are observed. Serum transferrin receptor 1 (TfR1) level is a test to differentiate IDA from chronic inflammation or infection.[23] In ID, serum TfR1 levels increase to take up more iron into the cell, and in thalassemia, an increase in erythroid progenitor cells is accompanied by the TfR1 increase. Serum transferrin receptor 1 is not affected by inflammation and infection. In addition, the TfR1/log ferritin ratio has high sensitivity and specificity in distinguishing IDA from inflammation and infection. However, because TfR1 testing is an expensive method, it cannot be routinely performed. In ID anemia, routine bone marrow examination is not recommended. However, when performed, decreased iron stores can be demonstrated by iron staining. Although suppression of hepcidin (≤10 ng/mL) is indicative of IDA, its elevation suggests inflammatory anemia, which is not easily available.[24]

In addition, the American Academy of Pediatrics suggests 3 parameters that provide differential information on iron status: serum ferritin (SF), reticulocyte hemoglobin concentration (CHr), and TfR1 concentrations. The CHr assay provides a measure of the iron available to cells recently released from the bone marrow. Therefore, the following combination of assays can be used to diagnose ID: (1) SF and CRP measurements or (2) CHr measurements. A low CHr concentration has been shown to be the strongest predictor of ID in children. Moreover, a hematologic response, i.e., a 1 g/dL increase in hemoglobin concentration after 1 month of therapeutic iron supplementation, confirms the diagnosis IDA.[4]

DIFFERENTIAL DIAGNOSIS OF IRON DEFICIENCY

Other causes of hypochromic microcytic anemia should also be considered in the differential diagnosis. These conditions include α- or β-thalassemia carriers, hemoglobinopathies such as hemoglobin E, S/β, chronic disease anemia, sideroblastic anemia, atransferrinemias lead and aluminum poisoning, and copper deficiency.[11] Table 3 summarizes laboratory features for the differential diagnosis of common causes of hypochromic microcytic anemia from IDA. While the red cell count is decreased in ID anemia, and it is usually high (>5 × 10^{12}/L) or normal in thalassemia carriers. While the Mentzer index, which is calculated by dividing MCV by red cell count (×10^{12}/L), is less than 13 in thalassemia carriers, a value above 13 suggests IDA. In patients with β-thalassemia carriers and ID, a normal HbA2 percentage does not exclude a β-thalassemia carrier,

Table 3. Differential Diagnosis of Common Causes of Hypochromic Microcytic Anemia from Iron Deficiency Anemia			
	IDA	**β-thalassemia Carriers**	**Chronic Disease Anemia**
Hemoglobin (g/dL)	Low	Normal/Low	Low
MCV	Low	Low	Normal/low
RDW	High	Normal/high	Normal/high
Serum ferritin	Low	Normal	High
Serum iron	Low	High	Low
TIBC	High	Normal	Low
Transferrin saturation	Low	Normal/high	Low
FEP	High	Normal	High
HbA_2	Low/normal	High	Normal

FEP, free erythrocyte protoporphyrin; IDA, iron deficiency anemia; MCV, mean corpuscular volume; RDW, red blood cell distribution width; TIBC, total iron binding capacity.

Table 4. Potential Problems in Patients Who Do not Respond to Oral Iron
Compliance problems or inadequate dose
Malabsorption (celiac disease, giardiasis)
Medications (antacids, proton pump inhibitors, tannin, phytate)
Blood loss (gastrointestinal, menstrual)
Concomitant infection or inflammation (inhibits response to iron)
Concurrent vitamin B12 or folate deficiency
Lead poisoning
Misdiagnosis

due to ID may limit the production of HbA2. Potential problems in patients who do not respond to oral iron are summarized in Table 4. Moreover, jaundice and splenomegaly suggest hemolytic anemia, bleeding symptoms suggest coagulopathy or bone marrow infiltration, fever, recent weight loss, night sweats, hepatosplenomegaly, and/or lymphadenopathy suggests lymphoma or leukemia.[14] Additionally, von Willebrand's disease should be considered in girls with heavy menstrual bleeding. In order to prevent anemia due to excess blood loss, these girls should be treated relevantly.

MANAGEMENT OF IRON DEFICIENCY

The causes of ID should be identified and corrected, and the patient should be fed iron-rich foods. Beverages containing vitamin C, which increase iron absorption, are recommended with meals, while tea, coffee, milk, and yogurt, which impair absorption, should be avoided. The bioavailability of foods containing heme iron is 10 times higher than other iron-containing foods. For girls with abnormal uterine bleeding, estrogen- or progesterone-containing hormonal treatment may be helpful to reduce bleeding.

Oral replacement is always the first choice for ID. Preference should be given to drugs in the form of drops, syrup, or capsules containing +2-valent iron such as ferrous sulfate and ferrous fumarate. There is no evidence that supplementation with any other vitamin improves response to iron therapy. Formulations containing ferric (+3) iron are more comfortable to drink since they taste like sweet syrup, but it should be kept in mind that treatment with +3 iron is effective over a longer period of time and may lead to failure. The family and child should be informed that the medications may have a bad taste and may cause nausea, vomiting, dyspepsia, and discoloration of teeth and stool.[25] Empirically, 2-3 mg/kg/day is given for ID and 3-6 mg/kg elemental iron is given in IDA once daily or in divided doses. However, recent studies report that the morning iron dose increases serum hepcidin levels, which can be high for up to 24 hours and therefore decreases the absorption of oral iron during the day.[26] It is recommended that lower daily doses can be given to increase iron absorption and that single daily doses should be preferred. It should be administered on an empty stomach or 2 hours after a meal. In patients who cannot tolerate it in this manner, a dose reduction, administration after a meal, or a better tasting formulation may be tried. Because a rapid hematologic response can be achieved in IDA, packed red cells should be used only in the presence of heart failure or hypoxia. Unless there is active bleeding, transfusion should be administered slowly to avoid heart failure.

Assessment of response to treatment is also an indicator of confirmation of the diagnosis. In children with mild anemia, a complete blood count examination after 1 month may be sufficient. Whereas in children with severe anemia, the reticulocyte count should be checked between 7 and 10 days after treatment. In patients with severe anemia, an increase in hemoglobin of more than 2 g/dL should be expected during the first month of treatment. When a normal hemoglobin level is achieved, the recommended drug dose should be halved to replenish iron stores and treatment should be continued for at least 3 months.

However,

1. Parenteral therapy is preferred in cases of non-compliance and cannot tolerate or do not respond to oral iron therapy.
2. Parenteral iron therapy is preferred for intestinal disturbances that cause problems with iron absorption, such as celiac disease. In addition, oral administration of iron in inflammatory bowel disease may exacerbate the disease.
3. In chronic bleeding, intramuscular or intravenous administration may be preferred, as oral therapy may not compensate for the loss. It is recommended that the patient requiring parenteral iron therapy be evaluated by a hematologist.

The amount of iron to be administered parenterally can be calculated using the following formula: Iron deficit (mg) = [weight (kg) × {target Hb – actual Hb (g/dL)} × 2.4]+[15 mg × weight (kg)]. The resulting amount of iron can be administered at 50-100 mg every other day.

a. Intramuscular: Intramuscular therapy is safe and effective. However, intramuscular injection is not generally preferred but may be administered with caution in compelling cases because children do not have much muscle mass, absorption is variable with intramuscular injection, and causes pain and skin discoloration. Iron dextran can be administered as intramuscular therapy.
b. Intravenous: The polynuclear iron hydroxide–sucrose complex is suitable for intravenous use. Iron dextran is not recommended for intravenous use because it is less safe and requires a test dose. The total dose is administered as an intravenous infusion in divided doses, and the daily dose should not exceed 100 mg. Side effects of parenteral therapy include anaphylaxis, joint and muscle pain, fever, skin flushing, nausea, vomiting, rash, and hypotension.[27]

If the patient has anemia severe enough to cause cardiac failure, has a pulmonary infection associated with hypoxia, has a hemoglobin level of 4 g/dL or less, or is scheduled for emergency surgery, packed red blood cells may be administered. In these cases, the transfusion volume should be kept low, e.g., 2-3 cc/kg.

CONCLUSION

Identification and follow-up of children at high risk for ID and iron supplementation will reduce the incidence of ID. Early identification of ID may improve neurodevelopmental problems due to ID without permanent damage. Ferrous iron

supplements can be used at relatively lower doses and once a day as oral therapy. Information about the side effects of drug treatment increases adherence to therapy. In addition to drug treatment, recommendations for an iron-rich diet can prevent the recurrence of IDA. In cases where oral treatment does not respond well, there are drugs with proven safety for intravenous treatment.

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