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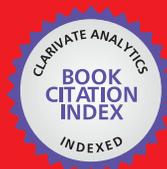International authors and editors

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Iron Deficiency Anemia in Children

Jelena Roganović and Ksenija Starinac

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Abstract

Iron deficiency and iron deficiency anemia remain a major and global public health problem that affects particularly infants, young children, and women of childbearing age in developing countries. The prevalence of iron deficiency anemia is still common in industrialized countries despite efforts to improve public awareness and strengthen programs for the prevention and control of iron deficiency. The most common risk factors for iron deficiency in early childhood are rapid growth, perinatal risk factors, poor dietary intake, and gastrointestinal blood loss due to excessive consumption of cow's milk. Iron deficiency and iron deficiency anemia cause a wide variety of symptoms and changes in many different tissues. The most concerning consequences of iron deficiency in children are the alterations of cognitive, motor, and behavioral performance. Persistent neurocognitive changes despite iron repletion have increased the importance of prevention and early detection of iron deficiency. The main principles of treatment include investigation and elimination of the underlying cause, iron supplementation, improvement of nutrition, and education of the patient and family. Oral iron supplements are desirable as first-line therapy. Follow-up is very important to confirm the diagnosis and to ensure that anemia is adequately treated.

Keywords: iron deficiency, anemia, child, prevention, iron supplementation

1. Introduction

Iron deficiency is the most common micronutrient deficiency worldwide and one of the most important public health problems, affecting approximately 25% of the world's population according to the World Health Organization (WHO). Iron deficiency is the most common in preschool children and women of childbearing age, particularly in regions of Asia and Africa with poor access to iron-rich foods [1, 2]. There are lower rates of iron deficiency in developed countries such as the United States and other industrialized regions with healthy food rich in

nutrients. However, the problem still exists and can have a great impact on mental and physical development, health maintenance, and the quality of life of affected children.

2. Epidemiology

Approximately 8% of toddlers in the United States have iron deficiency, and 2–3% have iron deficiency anemia (IDA) [3]. As age increases, prevalence decreases until adolescence. Sixteen percent of adolescent girls have iron deficiency, and 3% have IDA [4]. Among American females aged 12–15 years, the incidence of iron deficiency was 9% and the incidence of IDA was 2%; in the age group 16–19 years, the incidence was 11 and 3%, respectively [5]. Less than 1% of adolescent males had iron deficiency. Higher incidence of iron deficiency was found in both male and female adolescents in some other countries [6, 7]. The rate of iron deficiency did not decline much during the last 40 years, but there were significant improvements in some subgroups of young children. For example, in children aged 12–24 months, iron deficiency rates declined from 23 to 11% between two study periods [3].

The prevalence of iron deficiency in the United States is higher in children who live in poverty, in low-income families, and in immigrant groups. The highest prevalence was shown in children with African-American and Hispanic origin [3, 8]. Other risk factors associated with higher prevalence of IDA are low birth weight, prematurity, and childhood obesity [3, 8, 9]. These high-risk pediatric subgroups should undergo screening.

Pinhas-Hamiel and co-workers showed that the prevalence of iron deficiency was significantly associated with increased body mass index (BMI) [10]. Obesity was a risk factor in both males and females, but it was about three times higher in girls [10, 11]. It is unclear why obesity is linked to iron deficiency and IDA, but low-quality foods and increased needs comparing to body weight may be connected.

Adolescent athletes, vegetarians, adolescents with chronic illnesses, heavy menstrual blood loss (>80 ml/month), or children who are underweighted or malnourished are at higher risk for iron deficiency and IDA, and they should also have laboratory screening for anemia [12, 13].

In developing countries, where diets do not contain sufficient red meat, IDA is approximately seven times more frequent than in Europe or North America. Despite the fact that there is enough dietary iron in some cases, this is the case because heme iron is absorbed better than nonheme iron. IDA was found in 2/3 of children and adolescents in Nepal and in Sudan [14], and in 48.5% of Egyptian children in 2005 [15]. Parasites like hookworm can worsen iron deficiency due to profound gastrointestinal blood loss.

Neonates have total body iron of 250 mg (80 mg/kg), obtained from maternal sources. In the first 6 months of life, during the period when the infant gets iron-deficient milk diet, this amount decreases to 60 mg/kg. Infants fed with cow's milk are at greater risk to develop serious IDA because calcium from cow's milk is competing with iron for absorption. Children should get 0.5 mg more iron than is lost daily in order to maintain a normal body iron of 60 mg/kg.

The prevalence of iron deficiency exceeds 50% in countries with limited food and nutrient sources, such as most countries in Africa, Southeast Asia, and Latin America [16]. The prevalence of anemia ranges from 45 to 65% in children, 20 to 60% in women, and 10 to 35% in men [1]. Half of these cases are presumed to be caused by iron deficiency.

The prevalence of IDA is still high in infancy and preschool children, despite improvements in public health awareness, increased breastfeeding rate, and the presence of iron-fortified foods in diet [17, 18]. All these facts emphasize the importance of constant surveillance and early detection, prevention, and intervention toward iron deficiency in childhood, particularly in high-risk groups. Special attention should be paid to discover and treat iron deficiency during pregnancy and the earliest periods of life, because severe iron deficiency can have a great impact on child's growth, development, and learning skills.

3. Definitions

Iron deficiency is a condition when the body lacks sufficient iron to maintain normal physiological functions. It is defined as decreased total body iron or, in some cases, by serum ferritin level <12 mg/l in children up to 5 years and <15 mg/l in children 5 years and older. Although the serum ferritin level is useful in defining iron deficiency, this definition can be considered only if other conditions that can affect ferritin levels (i.e., inflammation or liver disease) are absent. For children less than 5 years of age with concurrent infection, serum ferritin concentrations <30 mg/l are reflective of depleted iron stores [19].

Anemia is defined as a hemoglobin concentration more than 2 standard deviations below the mean reference value for age- and sex-matched healthy population. WHO hemoglobin thresholds used to define anemia in different age groups are [2]:

- children 6 months to 5 years: 11 g/dl;

- children 5–12 years: 11.5 g/dl;

- children 12–15 years: 12 g/dl;

- nonpregnant women: 12 g/dl;

- pregnant women: 11 g/dl; and

- men ≥15 years: 13 g/dl.

IDA develops when body iron is too low to maintain normal red blood cell (RBC) production. IDA in young children (up to 5 years) is defined as the presence of ferritin level <12 mg/l and hemoglobin level <11 g/dl, in the absence of other conditions that can affect these findings [20].

The terms "iron deficiency" and "IDA" are often used in the same context. However, iron deficiency without anemia is three times as common as IDA. If iron requirements are below iron intake, total body iron reduces gradually. Hemoglobin levels are initially normal, reflecting the stage when iron deficiency exists in the absence of anemia. At that point,

ferritin level and transferrin saturation are reduced. As total body iron decreases and iron stores are exhausted, hemoglobin levels drop below normal values. Thus, iron deficiency is defined as reduced body iron but hemoglobin levels are still above the cut-off value for anemia. Worsening of that condition leads to iron-deficient erythropoiesis and finally to development of IDA.

4. Pathophysiology

Iron is an essential micronutrient in the human body. It plays an important role in many metabolic processes, such as oxygen transport, electron transport, and DNA synthesis. Iron is a component of many cellular proteins and enzymes. Heme proteins, hemoglobin and myoglobin, contain about 3/4 of total body iron. The rest of body iron is stored in ferritin and hemosiderin, and about 3% is part of enzyme systems, such as catalase and cytochromes [21]. Iron is mostly recycled from senescent RBCs by macrophages. Only a small proportion of total body iron enters and leaves the body on a daily basis. Consequently, mechanisms that affect intestinal absorption and intercellular iron transport have great impact on iron balance. The serum iron concentration is regulated by absorptive cells in the proximal small intestine, which can regulate iron absorption to compensate for iron body loss. There are three different pathways of iron uptake in the small intestine: the heme pathway and two specific pathways for ferric and ferrous iron, respectively.

Enterocytes absorb heme iron and nonheme iron noncompetitively. Dietary iron contains both chemical forms of iron. Heme iron is mainly found as ferrous iron (Fe^{2+}), while the most part of nonheme dietary iron is ferric iron (Fe^{3+}). When heme enters the enterocyte, it is degraded by heme oxygenase with release of iron. It passes the basolateral membrane of the enterocyte and competes with nonheme iron to bind transferrin in the plasma. The way of nonheme iron transport in the body is still not known. The concentration of iron in the enterocytes depends on the body's needs for iron. Individuals who are iron-deficient have a small amount of iron in enterocytes, while those who have sufficient body iron have higher amounts of iron in the absorptive intestinal cells. Iron in the enterocyte regulates absorption by either up-regulation of receptors or saturation of an iron-binding protein, or both. Iron that is delivered to other nonintestinal cells in the body is bound to transferrin. There are two pathways through which transferrin iron can be delivered into nonintestinal cells: classical transferrin receptor pathway and the pathway independent of the transferrin receptor.

In adults, only 5% of total body iron requirements is from different food sources. This amount is the same as iron loss, which is mainly from the gastrointestinal tract. The majority (95%) of iron comes from the breakdown of old RBCs. In children, approximately 30% of iron comes from diet, probably due to fast growth in pediatric age [21, 22].

There are three major factors that can influence intestinal iron absorption: iron stores in ferritin and transferrin, erythropoietic rate, and bioavailability of iron in foods. When iron stores decrease, receptors in the intestinal mucosa increase in order to raise iron uptake. Iron absorption also increases when there is increased or ineffective erythropoiesis.

5. Risk factors

5.1. Perinatal risk factors

During the intrauterine period, the only source of iron is the iron that is crossing through the placenta. The majority of healthy infants have iron stores of about 80 mg/kg, and 2/3 of total iron is bound in hemoglobin molecules. Normal hemoglobin concentration is 15–17 g/dl. Healthy infants have enough body iron for the first 5–6 months of life [22, 23]. There are some conditions that can reduce iron stores at birth or can act through other mechanisms, thus increasing the risk for developing IDA during the first months of life. These conditions are maternal iron deficiency, prematurity, administration of erythropoietin for anemia of prematurity, fetal-maternal hemorrhage, twin-twin transfusion syndrome, other perinatal hemorrhagic events, and insufficient intake of dietary iron during early infancy. Delayed clamping of the umbilical cord (approximately 120–180 seconds after delivery) can improve the amount of iron and significantly reduce the risk of IDA [24].

Deficiency of iron during pregnancy increases the risk of iron deficiency in the infancy. A study of Kumar et al. showed that iron in the cord blood sample was in correlation with mother's hemoglobin and ferritin levels [25]. The content of iron in breast milk was reduced in mothers with severe anemia, but it was normal in mothers with mild or moderate anemia. It is recommended to implement iron supplementation during pregnancy in the populations with high prevalence of maternal IDA. It is also important to provide different kinds of iron-fortified foods for pregnant women who are at risk to develop IDA [26].

Prematurity is one of the risk factors for IDA because premature infants have smaller total blood volume at birth compared to healthy term infants, decreased ferritin concentrations, poor gastrointestinal absorption, and increased blood loss through phlebotomies [27]. Iron is mostly accumulated during the third trimester of gestation that is shorter in preterm infants. There is also increased risk for iron deficiency after use of erythropoietin for the prevention and the treatment of the anemia of prematurity [23].

Chronic fetal-maternal hemorrhage and twin-twin transfusion syndrome (TTTS) can reduce iron stores and cause anemia in term or premature infants. A small amount of fetal blood (<0.1 ml) is commonly found in maternal circulation. Causes of increased loss of fetal blood into the maternal circulation are seen as a result of trauma, placental abruption, or may be spontaneous and idiopathic. Manifestations of fetal-maternal hemorrhage depend on the amount and the rapidity of blood loss [28]. TTTS is a rare complication of monochorionic twins (or higher multiple gestations). It is the result of blood transfusion from one twin (donor) to another twin (recipient) through placental vascular anastomoses. The donor twin is smaller and often anemic, and the recipient twin is often plethoric with hemoglobin differences greater than 5 g/dl. Advanced stages of TTTS have 60–100% mortality rate, and fetuses who survive are at risk of severe cardiac, neurologic, and developmental disorders [29].

5.2. Dietary factors

Feeding and all dietary aspects are very important in early infancy and childhood because they can greatly impact development of IDA. There are many dietary factors that can affect

iron metabolism. The most common factors are poor iron intake, decreased iron absorption, consumption of unmodified cow's milk before 12 months of age, and occult intestinal blood loss due to cow's milk protein-induced colitis [30].

Poor iron intake in infancy usually occurs when babies are fed with infant formulas or transitional foods which are not fortified with iron. In the study from Chile, the prevalence of IDA was higher in infants fed with the formula without iron (20%), much lower in those fed with iron-fortified formula (0.6%), and medium in infants fed with human milk (15%) [31]. In another study, an increased prevalence of IDA in infancy was observed in infants fed with nonformula cow's milk > 600 ml or more daily or > 6 breast feeds per day [32]. The amount of iron in human milk is highest during the first month of life, but gradually decreases in the following period. This amount varies among individuals. Maternal diet does not affect iron amount in the human milk.

Intestinal iron absorption depends on the form of iron in the foods. Dietary sources of heme iron, such as fish, meat, and poultry, have higher bioavailability of iron compared to nonheme sources of iron, such as fruits, vegetables, and grains. There are also various components of food that influence intestinal iron absorption. Vitamin C increases iron absorption from bread, cereals, fruits, and vegetables (nonheme iron) but has little effect on the absorption of heme iron. IDA is a common problem in children who follow a vegetarian diet. Intestinal absorption of ferrous and ferric iron is inhibited by tannins in different kinds of teas, foods rich in phosphates, oxalates, carbonates, and phytates (seeds and grains). Purified heme is absorbed poorly because heme polymerizes into macromolecules. Globin prevents the formation of insoluble heme polymers so that it remains available for absorption. Peptides from the degraded globin bind to iron and prevent iron polymerization and precipitation. Different forms of iron can be absorbed better when given together (i.e., spinach with meat).

One of the most important risk factors for IDA is early introduction of unmodified (nonformula) cow's milk. It increases the risk for intestinal blood loss in infants compared with the formula or breast feeding, mainly due to colitis [33]. Daily intake of 720 ml or more of cow's milk in preschool children is associated with increased risk for iron deficiency. The reasons are low concentration of iron in cow's milk, low bioavailability of iron, and possibly increased intestinal blood loss [34]. Sutcliffe et al. reported increased risk for iron deficiency in children with continued bottle-feeding compared with children with cup-feeding in the age of 2–3 years, mainly due to the greater volumes of cow's milk in bottle-feeding [35].

5.3. Gastrointestinal disease

Dietary iron is absorbed mainly throughout duodenum. Gastrointestinal malabsorption of iron occurs in diseases that affect this portion of the intestine, including celiac disease, Crohn disease, giardiasis, and resection of the proximal small intestine. In children, anemia secondary to iron, folic acid, and vitamin B12 malabsorption is a common complication of celiac disease, and further screening with tissue transglutaminase antibodies has been strongly recommended [36]. Conditions that cause gastrointestinal blood loss are also associated with iron deficiency. These include cow's milk protein-induced colitis, inflammatory bowel disease (IBD), duodenal/gastric ulcers, and chronic use of nonsteroidal anti-inflammatory drugs

or aspirin. Iron deficiency occurs in about 60–80% of patients with IBD. Anemia of chronic disease, vitamin B12 deficiency, folic acid deficiency, and hemolysis contribute to the development of anemia in patients with IBD [37, 38].

6. Screening recommendations

Routine screening for IDA should be obtained in children 6–24 months of age. Screening consists of reviewing risk factors during any possible occasion or visit (risk assessment), and laboratory testing (laboratory screening) at least once during the mentioned period. Screening is recommended at all times for all infants and children who have any risk factor (malnutrition, low birth weight, prematurity, signs and symptoms of IDA, or living in the area with high prevalence of iron deficiency).

6.1. Risk assessment

Review of risk factors in all children is recommended at 4, 15, 18, 24, and 30 months, at 3 years, and once yearly afterward. This is currently the most important and valuable screening tool, more useful than laboratory testing of hemoglobin. Risk assessment consists of focused dietary history. The most vulnerable groups are children with the history of prematurity or low birth weight, infants using low-iron formula, nonformula cow's milk, soy milk or goat's milk before 12 months of age, infants having less than two iron-rich meals daily after 6 months of age, preschool children drinking more than 600 ml milk per day, or having less than three iron-rich meals daily.

6.2. Laboratory screening

American Academy of Pediatrics (AAP) suggests laboratory testing as the screening tool for iron deficiency at 1 year of age [30]. Universal laboratory screening is recommended for all children 9–12 months of age. Additional laboratory screening is recommended for children with risk factors for iron deficiency and IDA. There are two groups of children that should undertake additional laboratory screening:

- children with high risk for iron deficiency—repeated laboratory testing at 15–18 months of age or when some risk is identified; and

- children with special health needs (chronic diseases, inflammatory disorders, restricted diets)—repeated laboratory testing in the period of early childhood (2–5 years of age).

Laboratory screening in most cases includes complete blood count, which includes hemoglobin, hematocrit, mean corpuscular volume (MCV), and red blood cell distribution width (RDW). The minimum laboratory screening is measurement of hemoglobin with the normal value greater than 11 g/dl.

Laboratory testing of serum ferritin at the time of the first screening is the major diagnostic tool in children with risk factors for iron deficiency and IDA [30]. Ferritin levels should

be always evaluated carefully because ferritin is nonspecifically elevated in a wide variety of inflammatory conditions. A C-reactive protein can help to validate the results of serum ferritin levels. Other screening measurements that can be taken into account as a different approach for iron deficiency include reticulocyte hemoglobin concentration and combination of soluble transferrin receptor and hemoglobin [39].

It is recommended by AAP to perform risk assessment once a year during the period of adolescence. Adolescents with risk factors (those with a history of IDA, low-iron diet, or girls with heavy menstrual bleeding) should have laboratory testing for anemia [40]. Considering different opinions on screening recommendations in adolescents, each physician should personally decide about the screening process based on the risk factors. Laboratory testing should be done every 5 years starting from age 13 in girls, and at least once during the rapid growth period in boys. Children with any risk factor (increased physical activity, special diets, obesity, malnutrition, chronic illnesses, and heavy menstrual bleeding in girls) should be monitored more frequently [12].

There is some controversy on routine screening for iron deficiency in areas with low rates of iron deficiency and IDA (i.e., United States). Studies provide little evidence that routine screening or iron treatment improves child's growth and neurodevelopmental outcome. On the other hand, routine screening is recommended because of the important health benefits. Besides, a physician should not decide about screening program only based on symptoms and risk factors in a child. Those who favor screening for iron deficiency in the adolescent period list high prevalence of anemia in that population and adverse consequences of iron deficiency [41]. The screening tests are generally minimally invasive (blood sample), and therapy for IDA is safe.

7. Prevention

Many recommendations for prevention of iron deficiency and IDA have been published, and the most commonly used are those provided by WHO and AAP. Widely used approaches include iron-fortified foods in a diet, iron-rich formulas, introduction of cow's milk in a diet from 12 months of age, screening for iron deficiency, and iron prophylaxis in infants [30].

It is important to emphasize that only a fraction of dietary iron is absorbed from food, depending on bioavailability (dietary iron absorption). Human milk contains only 0.3–1.0 mg/l of iron, but the bioavailability of iron is 50%, while milk formulas contain 12 mg/l of iron with bioavailability of iron 4–6% only [42]. As mentioned above, dietary iron has two main forms: heme and nonheme iron. Plants and iron-fortified foods contain nonheme iron only, whereas meat, seafood, and poultry contain both heme and nonheme iron. Heme iron has higher bioavailability than nonheme iron. The bioavailability of iron is approximately 14–18% from mixed diets, and 5–12% from vegetarian diets. Daily iron requirements vary depending on age and gender. Requirements for iron are 0.6 mg/day in healthy infants and 0.8 mg/day in preadolescent children. Adult males need 1 mg/day of iron, and adult females need 1.5 mg/day [43]. The recommended dietary iron for healthy full-term infants (from birth to 12 months

of age) is 1 mg/kg/day (maximum 15 mg); for premature infants 2–4 mg/kg/day (maximum 15 mg); for toddlers 1–3 years of age 7 mg/day; for children aged 4–8 years 10 mg/day; for children aged 9–13 years 8 mg/day; for adolescent boys aged 14–18 years 11 mg/day, and for adolescent girls aged 14–18 years 15 mg/day [43]. Boys have increased requirements during pubertal growth because of expanding blood volume and increase in hemoglobin concentration. Increased requirements in girls during puberty are mostly due to menstrual blood loss, although the loss differs in various individuals. Besides, adolescent girls more often have a tendency to eat food that contains less iron and to avoid high iron-containing foods, contributing to iron deficiency [44].

7.1. Recommendations for supplementation

Infants who are not breastfed, obtain sufficient amount of iron from iron-fortified formula. Breastfed infants should receive an additional source of iron (as iron supplement or complementary food) in these doses:

- Full-term breastfed infants should receive an iron supplement from the age of 4 months (1 mg/kg/day, maximum 15 mg) until the infant has sufficient iron-rich complementary foods in a diet.

- Premature breastfed infants should receive an iron supplement starting from the age of 2 weeks (2–4 mg/kg/day, maximum 15 mg) throughout the first year of life (as supplements or iron-fortified formula).

Supplementation of iron is necessary to meet requirements in infants from populations with high rates of iron deficiency and IDA. In a prospective randomized trial of early versus late iron supplementation in low-birth-weight infants, infants who received early iron supplementation (started when feedings reached 100 ml/kg/day) had lower risk of infection and lower number of blood transfusions compared to infants who received late supplementation (started at 61 days of age) [45]. In a study from India that included breastfed infants at the age of 4–6 months, oral iron supplementation resulted in better growth, especially in infants who had anemia or were otherwise nutritionally deficient [46].

Prevention of iron deficiency and IDA varies by geographical region, age group, and other conditions. In countries with high prevalence of IDA, comprehensive strategies and interventions for high-risk groups are implemented, in particular for young children, adolescent girls, women in reproductive age, and pregnant and breastfeeding women. In some regions, food fortification with iron, control of helminth infection, and control of malaria are effective approaches to prevent IDA [17].

7.2. Dietary recommendations

The optimal way to reach iron requirements is an improvement of food quality. In countries with low prevalence of iron deficiency, recommended dietary intake should assure expected iron requirements. Exclusive breastfeeding is recommended for the first 4–6 months of life. Preterm breastfed infants should receive an iron supplement from 2 weeks of age. Additional

source of iron should be given to infants starting at 4 months of age, first as an iron supplement, followed by iron-fortified foods (two or more meals/day meet the expected requirements for iron). Partially breastfed and nonbreastfed infants should consume exclusively iron-fortified formulas [47].

Starting from the age of 6 months, infants should receive one feeding rich in vitamin C (green vegetables, fruits, and juices) daily. After 6 months of age, meat should be introduced in a diet. Heme iron (meat and fish) is more bioavailable than nonheme iron (vegetables and cereals). Combining heme foods with nonheme foods also increases the absorption of iron [48]. Moreover, consumption of meat meets many requirements besides iron.

Infants should not be given nonformula cow's milk until the age of 12 months. The higher concentration of calcium in cow's milk inhibits absorption of iron. Children aged 1–5 years should drink less than 600 ml of milk daily. Besides, they should take enough iron-containing foods to fulfill daily iron requirements. Children, who do not eat at least 2 or 3 iron-rich foods every day, may have inadequate iron intake and may need iron supplementation [49].

8. Signs and symptoms

IDA is the final stage of iron deficiency, and the first one that can recover with iron supplementation. Iron deficiency without anemia may also be associated with some clinical signs and symptoms, such as fatigue, cognitive dysfunction, or decreased energy.

The most common presentation of IDA in an asymptomatic infant or a child, who is well-nourished and otherwise healthy, is mild-to-moderate microcytic and hypochromic anemia. Slowly progressive paleness may sometimes be missed, but anemia also produces nonspecific pallor of the mucous membranes. Signs of epithelial tissues that may be associated with IDA are koilonychia, glossitis, and angular stomatitis. Severe form of IDA is much rare and is presented with poor feeding, irritability, lethargy, tachypnea, and cardiomegaly. Growth is impaired in children with severe IDA, and splenomegaly may be present.

Symptoms of IDA are presented by many body systems and functions of the affected child: impaired psychomotor and/or mental development, effects on immunity and susceptibility to infection, decreased exercise capacity, weakness, pica and/or pagophagia, headache, irritability, beeturia, and restless leg syndrome in older children. Some of these symptoms may lead to long-term consequences. Iron deficiency significantly contributes to thrombotic risk. In cases of severe IDA, some children may experience acute life-threatening conditions, including hypotension, tachycardia, tachypnea, respiratory distress, and congestive heart failure. The presence of one or more of these findings requires immediate hospital admission and prompt treatment. Severe IDA may rarely be associated with increased intracranial pressure, clinical signs of pseudotumor cerebri, or papilledema. All these symptoms resolve with iron supplementation [50].

8.1. Neurodevelopmental signs and symptoms

Impaired psychomotor and/or mental development is common in infants with iron deficiency, and neurocognitive impairment in adolescents with IDA [51–53]. Negative impact on social and emotional behavior may appear and can lead to the development of attention deficit hyperactivity disorder (ADHD) [54]. Mood swings are frequent. Children with iron deficiency get tired easier and faster, and play less compared to healthy children. Numerous randomized trials performed on different pediatric age groups showed that iron supplementation prevented or corrected neurodevelopmental delay. These studies were mostly performed in low- or middle-income countries [55–57]. In the study from Costa Rica, iron deficiency and IDA were more frequent in infants fed with nonfortified- iron formula. In these infants, psychomotor development declined at the age 9 and 12 months. There were not any significant changes in mental development and behavior [58]. Some other studies demonstrated that psychomotor impairment might not completely recover after treatment of moderate-to-severe IDA [56, 59–62]. Children who had iron deficiency at the inclusion in the study continued to have lower cognitive scores when tested at school age and in adolescence compared to children with good iron balance and no iron deficiency [59]. Children who were treated for iron deficiency during infancy had lower scores on electrophysiological tests on recognition memory at 10 years of age, comparing with children without iron deficiency during infancy. Behavioral tests showed similar results in these two groups [61].

The biologic basis of neurodevelopmental disorders is not fully understood. Iron deficiency decreases expression of dopamine receptors, disrupts function of several enzymes in the nervous system with subsequent alterations in brain energy, and decreases myelin formation. Myelination disruption or impairment can be associated with constant changes in transmission through auditory and visual systems. In a study from Chile, auditory brainstem responses (ABR) and visual evoked potentials (VEP) were measured in two groups of 4-year-old children: children who were treated for IDA in infancy and non-anemic children who also received iron supplementation [63]. Subtle auditory and visual dysfunction was demonstrated with longer VEP and ABR latencies in children who had IDA in infancy compared with control group.

The relationship between IDA and febrile seizures (FS) has been examined in several studies with conflicting results. Studies that suggest positive correlation between iron deficiency and FS aim that the possible mechanism is iron-dependent metabolism of some neurotransmitters [64, 65]. Other studies found no association between iron deficiency and FS [66]. Zehetner et al. showed that iron supplementation for 16 weeks in dosage 5 mg/kg/day reduced the severity and frequency of breath-holding spells in children with IDA [67].

8.2. Immunity and infection

Iron deficiency and IDA have numerous effects on immune system and susceptibility to infection. Iron deficiency in children can induce defective functions of leukocytes and lymphocytes, and defective production of interleukin (IL)-2 and IL-6 [68, 69]. On the contrary, iron overload can increase the risk of infections with specific types of bacteria. Accumulation of

iron in immune cells interferes with their antibacterial activity, and some bacteria grow well in an iron-rich environment. Besides, iron-binding proteins transferrin and lactoferrin have bacteriostatic effects, and these effects are lost when these proteins are saturated with iron [70].

Since both iron deficiency and iron excess can compromise cellular function, the levels of iron that cells are exposed to should be regulated precisely. In populations with high prevalence of iron deficiency and IDA, iron supplementation has different effects on susceptibility to infection and immunity. Low iron status may protect against malaria infection, but malaria in turn is linked with anemia, and changes in iron metabolism during a malaria infection may modulate susceptibility to co-infections [71]. Recent study of Zlotkin and coworkers showed that iron supplementation did not increase the risk of malaria infection [72].

8.3. Exercise capacity

Iron is an essential cofactor in aerobic metabolism. In IDA muscles are forced to depend on anaerobic metabolism more than they do in healthy nonanemic individuals. Iron deficiency leads to decreased exercise capacity in children, especially adolescent athletes. IDA is associated with decreased work capacity [73, 74].

8.4. Pica and pagophagia

Pica refers to unusual appetite for substances that are not food. In children, pica is often associated with iron deficiency and IDA [75]. The most common form of pica is starch or clay ingestion. Both substances decrease absorption of dietary iron. Pagophagia is a particular form of pica characterized by repetitive and compulsive ingestion of ice, freezer frost, or iced drinks. Some children prefer cold vegetables instead of ice. Pagophagia is very common in iron deficiency without anemia and is present in a half of patients with IDA. It responds to iron supplementation very fast, earlier than hemoglobin recovery [76]. The mechanism through which iron deficiency causes pagophagia is unclear. Biochemical processes involving the central nervous system might elucidate the underlying mechanism. Pica is not specific for iron deficiency. It can be found in children with developmental disabilities, such as intellectual disability or autism. It is also described in children after brain injury [77].

8.5. Thrombosis

Both iron deficiency and overload have been associated with an increased thrombotic risk in experimental and clinical studies. It has been reported that IDA is associated with cerebral vein thrombosis [78]. In Canadian study, children with arterial or venous stroke who were previously healthy, had ten times more chance to have IDA than children without stroke [79]. The mechanism of this association is complex. It may be related to reactive thrombocytosis that is often finding in IDA. Iron deficiency may contribute to a hypercoagulable state by affecting blood flow patterns. Besides, IDA with hypoxia could precipitate situations of increased metabolic stress (i.e., infections) in particularly vulnerable areas of the brain supplied by end arteries [80].

8.6. Beeturia

Beeturia is defined as pink or red urine after the ingestion of beets. It is most common in individuals with iron deficiency [81]. This manifestation is caused by increased intestinal absorption and increased excretion of the red pigment betalaine (betanin). The pigment is decolorized by ferric ions, and urine excretion of betalaine is increased in iron deficiency.

8.7. Restless leg syndrome

This syndrome is a common sleep-related movement disorder characterized with uncomfortable urge to move legs. It occurs usually in the evenings, during periods of inactivity and rest, and is occasionally relieved by movement. Restless leg syndrome is associated with iron deficiency and is often improved by iron supplementation. The brain iron insufficiency has been documented by independently replicated cerebrospinal fluid and brain imaging studies for individuals without IDA [82].

9. Diagnosis

Detailed history and physical examination are essential in diagnosis of any disease. Detailed history from the parents is very important in diagnosing iron deficiency and anemia, especially about prenatal period and dietary habits including time of introducing solid foods.

Presumptive diagnosis of IDA is made by a combination of risk assessment and laboratory testing of hemoglobin level (<11 g/dl). In infants younger than 6 months, lower values of hemoglobin are observed because of physiological anemia, but hemoglobin values under 9 g/dl demand further evaluation in order to investigate if there is any accompanying factor. Other findings like low mean corpuscular volume (MCV) or high red cell distribution width (RDW) help to determine diagnosis. For a definite confirmation, additional steps are needed:

- Estimate risk factors for lead poisoning and measure blood lead level if it is indicated [30, 83].

- If there is no evidence of lead toxicity, and the most likely is dietary deficiency, apply empirical trial of oral iron supplementation*

  • For infants and toddlers less than 24 months of age with anemia—move directly to empirical trial because IDA is the most probable cause of anemia in this age group.

  • For children 24 months of age and older—besides hemoglobin, hematocrit, MCV, and RDW, evaluate reticulocyte count, peripheral blood smear, and stool for occult blood before starting empirical trial.

- In children with severe anemia, complicated medical history, and with signs and symptoms atypical for IDA, additional testing should be performed before starting treatment.

These additional steps are necessary because anemia is not sensitive or specific for iron deficiency. Two-thirds of children with iron deficiency in the United States are not anemic, namely 9% have iron deficiency and 3% are anemic. The prevalence of anemia is much higher in countries with higher rates of iron deficiency. On the other hand, two-thirds of anemic toddlers have some other cause of anemia apart from iron deficiency [30]. Evaluation for iron deficiency in adolescence should also include serum ferritin levels. IDA in adolescent is identified by hemoglobin concentration below 11 g/dl combined with low serum ferritin (<12 ng/ml).

9.1. Presumptive diagnosis and empirical trial

In infants and toddlers up to 24 months of age who have mild microcytic anemia with presumptive diagnosis of IDA based on screening results, the strategy of choice is therapeutic trial of iron [51]. The recommended dosage is 3 mg/kg of elemental iron, once or twice daily, best between meals (daily dosage 3–6 mg/kg). Ferrous sulfate is the convenient and most commonly used form of iron. If there is increase of hemoglobin concentration greater than 1 g/dl after 4 weeks of treatment, the diagnosis of iron deficiency is confirmed. In this case, iron supplementation and monitoring of the child with laboratory tests should be continued for at least several months, after hemoglobin levels reach normal range according to age.

IDA is less common in older children than in infants. Additional evaluation, besides complete blood count, MCV, and RDW, is suggested in children older than 2 years before starting iron treatment. This evaluation includes reticulocyte count, peripheral blood smear, and stool for occult blood. If results support the diagnosis of IDA, iron supplementation should be started. Additional evaluation is required only if there is no response to the treatment.

9.2. Laboratory testing

Basic laboratory testing in diagnosing IDA is complete blood count, including hemoglobin, hematocrit, MCV, and RDW. More detailed evaluation is needed for children with complicated medical histories, severe forms of anemia (hemoglobin <7 g/dl) or presence of features that are not typical for IDA. In these cases, several other tests should be performed: serum iron, serum ferritin, total iron-binding capacity (TIBC), transferrin saturation, and stools for the presence of occult blood. These tests, although nonspecific for IDA, can support the diagnosis of IDA in majority of cases. Low serum iron and ferritin levels with an elevated TIBC are diagnostic for iron deficiency.

Complete blood count shows the severity of anemia. Increased RDW is the first laboratory sign of iron deficiency [51, 84]. RDW is high in IDA because there is a wide variation in RBC size. MCV and mean corpuscular hemoglobin concentration (MCHC) are low. Platelet count is often elevated, and it normalizes after iron treatment. Peripheral blood smear is an important workup in patients with anemia. The first finding of IDA on peripheral smear is anisocytosis. Besides, RBCs are hypochromic and microcytic.

In infants and small children, iron deficiency is usually identified by a serum ferritin concentration <12 ng/ml. Diagnosis of IDA is based on the combination of hemoglobin concentration below 11 g/dl and serum ferritin levels below 12 ng/ml. However, when examining the

results, it must be taken into consideration that ferritin is an acute-phase reactant. Elevated serum ferritin levels have been associated with a wide range of conditions including inflammation, infection, chronic disease, and malignancy [85].

Free erythrocyte protoporphyrin (FEP), soluble transferrin receptor (sTfR), and reticulocyte hemoglobin content (CHr) are very useful and reliable laboratory tests to support the diagnosis of iron deficiency. FEP is a precursor of heme that normally occurs in very low concentration in RBCs. Elevated FEP values thus indicate early impairment of iron status and provide information about gradual changes in the iron supply. The sTfR refers to the cleaved extracellular portion of the transferrin receptor 1 that is released into serum. Iron deficiency causes overexpression of transferrin receptor and sTfR levels. The sTfR is regarded as a more stable marker of iron levels in an inflammatory state. CHr is a measure of early iron-deficient erythropoiesis. Reticulocyte hemoglobin content decreases earlier than hemoglobin content of RBC because normal life span of RBC is 120 days [86]. It has been shown that CHr measurement is more reliable and accurate laboratory test for the diagnosis of iron deficiency than hemoglobin level <11 g/dl, resulting in detection of greater number of patients with iron deficiency comparing to hemoglobin. On the other hand, greater number of falsely identified patients with iron deficiency was detected also by CHr, which is, although more sensitive, less specific than hemoglobin [87]. Serum transferrin receptor is found on reticulocytes and increased number of transferrin receptors is observed in IDA.

Some other types of anemia and other conditions that can be confused with IDA are mild hereditary anemias (alpha or beta thalassemia traits), mild anemia after recent infection or immunization, anemia of chronic disease, and combined nutritional anemias (malabsorption with vitamin B12 or folate deficiency). If the child does not respond to iron supplementation nor has some predisposing factor, other conditions should be considered.

10. Treatment

10.1. Oral iron therapy

For the successful treatment of IDA in infants and children, it is necessary to determine the appropriate dose and scheduling of oral iron therapy, apply dietary modifications together with iron supplementation, and follow-up the response to treatment.

Suggested dose for oral supplementation for infants and children with IDA is 3–6 mg/kg/day of elemental iron. Ferrous sulfate is generally recommended in a dose of 3 mg/kg of iron once or twice daily (maximum total daily dose, 150 mg of elemental iron). Elemental iron constitutes 20% of ferrous sulfate. Ferrous fumarate and ferrous gluconate are other forms of oral iron salts with different content of elemental iron. The iron supplement should be given between meals and preferably with juice because absorption of ferrous sulfate is increased when it is given with juice rather than with milk or other fluids. For maximum absorption of iron, administration 30–45 minutes before meal or 2 hours after meal is highly recommended.

The same doses of oral iron supplementation are recommended as a therapeutic trial for infants and young children with mild microcytic anemia and presumptive diagnosis of IDA [51]. Treatment should result in an increase of hemoglobin concentration greater than 1 g/dl within 4 weeks [30].

Side effects of oral iron preparations are gastrointestinal intolerance in higher doses, gray staining of teeth and gums (especially when given as a liquid preparation), effects on immune system, and susceptibility to infection.

10.2. Dietary changes

Dietary changes are necessary not only to prevent iron deficiency but also to add oral iron therapy. Following dietary changes are recommended for infants and children with proven or suspected IDA:

1. Infants should not be fed with unmodified cow's milk or low-iron formula. If infants are not breastfed or are partially breastfed, they should be fed with iron-fortified formula. Infants fed with cow's milk may have iron deficiency as a result of intestinal blood loss due to cow's milk protein-induced colitis. Lack of iron fortification in unmodified cow's milk contributes to iron deficiency state.

2. When iron deficiency is detected or suspected in a child older than 12 months, intake of cow's milk should be limited to 600 ml/day. Higher intake of cow's milk has been associated with higher risk for iron deficiency in several studies [34, 88]. Discontinuing bottle-feeding is also recommended because it generally helps in limiting milk intake [89]. If IDA is persistent and stool is positive for blood, all milk products should be stopped. In these cases, child should receive appropriate amount of calcium in a diet (calcium-rich foods).

3. Parents should be advised to modify child's diet in order to increase iron consumption. Infants 6 months and older should have appropriate intake of iron from complementary foods. Diet should contain cereals fortified with iron, food rich in vitamin C, and pureed meat.

10.3. Response assessment

Follow-up assessment is necessary to confirm that anemia has been caused by iron deficiency and the treatment was administered at correct dosage and timing. After 4 weeks of therapy, complete blood count should be done. It is recommended to perform evaluation when child is healthy and without viral infection that may cause acute decrease in hemoglobin.

If hemoglobin has increased at least by 1 g/dl after 4 weeks of oral iron supplementation, therapy should be continued, and hemoglobin re-evaluated every 2–3 months until hemoglobin reaches the normal value. Iron therapy should be continued additional 2–3 months to replace iron storage pools. Discontinuation of the treatment can lead to the recurrence of IDA.

If the appropriate response is missing after 4 weeks of treatment, additional evaluation of anemia is recommended. Possible causes of persistent or recurrent IDA are ineffective treatment, blood loss, malabsorption, or incorrect diagnosis. Parents should be asked whether the iron preparation has been given at the appropriate dosage and timing, whether suggested dietary modifications have been done, and if there were any intercurrent illnesses that could transiently decrease hemoglobin level. If the patient had no intercurrent illness and has been taking iron supplement in an appropriate dosage and timing, it is suggested to proceed with the following evaluation:

1. Evaluation for the type of anemia—Measuring of serum ferritin level, hemoglobin electrophoresis, vitamin B12, and folate can rule out the thalassemia trait, chronic disease anemia, and mixed nutritional deficiency. These conditions may imitate or complicate IDA. Very rare genetic mutations may interfere with iron transport and cause anemia similar to IDA, but without response to iron supplementation [90].

2. Evaluation for gastrointestinal blood loss—Stool should be tested for occult blood in a few separate samples. If the results are positive, it is recommended to assess further investigation for common causes of gastrointestinal blood loss, including cow's milk protein-induced colitis, celiac disease, and inflammatory bowel disease.

10.4. Parenteral iron therapy

Parenteral iron therapy is reserved for patients with severe forms of anemia who are intolerant to oral preparations, have poor response to oral supplementation, poor compliance, or malabsorption. Children with chronic gastrointestinal diseases as inflammatory bowel disease may require parenteral iron therapy because they often do not tolerate oral supplementation.

Most commonly used form of iron for parenteral use in children is low molecular weight iron dextran. It produces mild infusion reactions in less than 1% of patients and serious adverse effects are very rare [91]. Recently, ferric carboxymaltose administered as a short intravenous infusion without a test dose proved to be safe and highly effective in children and adolescents with IDA refractory to oral iron therapy [92]. Evaluation of treatment is usually performed at 4–12 weeks after the initial infusion.

10.5. Blood transfusion

Blood transfusion is rarely required in children with IDA. Transfusions are not considered necessary even with hemoglobin levels 4–5 g/dl, if the child is otherwise well. Blood transfusion should be administered only when there is an urgent need to restore oxygen-carrying capacity, i.e., in severe decompensated anemia. IDA develops gradually and over periods long enough to allow compensatory mechanisms to maintain intravascular volume. Consequently, there is a real risk of fluid overload with transfusion, and these patients should receive transfusion with caution. Standard of practice recommends slow transfusion of packed RBC volume of 5 ml/kg over 4 hours to avoid complications [93].

11. Conclusion

Iron deficiency is the most common nutritional deficiency in the world, affecting more than a quarter of the global population. Iron plays an essential role in many physiological functions, including oxygen binding and transport, cell growth and differentiation, gene regulation, enzyme reactions, and neurotransmitter synthesis. Iron deficiency develops in stages. In the first stage, iron requirement exceeds intake, causing depletion of bone marrow iron stores. As stores decrease, absorption of dietary iron increases compensatory. During later stages, deficiency impairs erythropoiesis, ultimately causing anemia.

Iron deficiency and IDA have many systemic effects, and the most concerning are diminished mental, motor, and behavioral functioning that might not be completely reversible after treatment with iron. Therefore, intervention should focus on primary prevention, which includes breastfeeding, fortification of foods with iron, use of iron-rich formulas when breastmilk is insufficient, and avoiding cow's milk before 1 year of age. Routine laboratory screening is recommended for all children 9–12 months of age. Risk assessment, consisting of focused dietary history, presents the most valuable screening tool, and additional laboratory screening is recommended for children with risk factors for iron deficiency and IDA.

Treatment starts with establishing the diagnosis. The main therapeutic principles are detection of the condition that causes iron deficiency, correction of underlying etiology, iron supplementation, dietary modifications, and education of families. Oral iron is the first-line therapy, giving in appropriate dose and scheduling. Adequate follow-up assessment for response is also important. If the appropriate response is missing, further evaluation should be obtained to rule out conditions that might simulate or complicate IDA.

Abbreviations

WHO   World Health Organization

IDA   Iron deficiency anemia

BMI   Body mass index

RBC   Red blood cells

TTTS   Twin-twin transfusion syndrome

IBD   Inflammatory bowel disease

AAP   American Academy of Pediatrics

MCV   Mean corpuscular volume

RDW   Red blood cell distribution width

ADHD   Attention deficit hyperactivity disorder

ABR   Auditory brainstem response

VEP   Visual evoked potential

FS   Febrile seizures

IL   Interleukin

TIBC   Total iron-binding capacity

MCHC   Mean corpuscular hemoglobin concentration

FEP   Free erythrocyte protoporphyrin

sTfR   Soluble transferrin receptor

CHr   Reticulocyte hemoglobin content

Author details

Jelena Roganović[1,2]* and Ksenija Starinac[3]

*Address all correspondence to: roganovic.kbcri@gmail.com

1 Clinical Hospital Center Rijeka and School of Medicine, University of Rijeka, Rijeka, Croatia

2 School of Medicine, University of Rijeka, Rijeka, Croatia

3 Service for Healthcare for Children and Adolescents, Kruševac, Serbia

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