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REVIEW ARTICLE

Iron Deficiency Anemia: An Updated Review

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Abstract: ***Background*:** Worldwide, iron deficiency anemia is the most prevalent nutritional deficiency disorder and the leading cause of anemia in children, especially in developing countries. When present in early childhood, especially if severe and prolonged, iron deficiency anemia can result in neurodevelopmental and cognitive deficits, which may not always be fully reversible even following the correction of iron deficiency anemia.

***Objective*:** This article aimed to familiarize physicians with the clinical manifestations, diagnosis, evaluation, prevention, and management of children with iron deficiency anemia.

***Methods*:** A PubMed search was conducted in February 2023 in Clinical Queries using the key term "iron deficiency anemia". The search strategy included all clinical trials (including open trials, non-randomized controlled trials, and randomized controlled trials), observational studies (including case reports and case series), and reviews (including narrative reviews, clinical guidelines, and meta-analyses) published within the past 10 years. Google, UpToDate, and Wikipedia were also searched to enrich the review. Only papers published in the English literature were included in this review. The information retrieved from the search was used in the compilation of the present article.

***Results*:** Iron deficiency anemia is most common among children aged nine months to three years and during adolescence. Iron deficiency anemia can result from increased demand for iron, inadequate iron intake, decreased iron absorption (malabsorption), increased blood loss, and rarely, defective plasma iron transport. Most children with mild iron deficiency anemia are asymptomatic. Pallor is the most frequent presenting feature. In mild to moderate iron deficiency anemia, poor appetite, fatigability, lassitude, lethargy, exercise intolerance, irritability, and dizziness may be seen. In severe iron deficiency anemia, tachycardia, shortness of breath, diaphoresis, and poor capillary refilling may occur. When present in early childhood, especially if severe and prolonged, iron deficiency anemia can result in neurodevelopmental and cognitive deficits, which may not always be fully reversible even with the correction of iron deficiency anemia. A low hemoglobin and a peripheral blood film showing hypochromia, microcytosis, and marked anisocytosis, should arouse suspicion of iron deficiency anemia. A low serum ferritin level may confirm the diagnosis. Oral iron therapy is the first-line treatment for iron deficiency anemia. This can be achieved by oral administration of one of the ferrous preparations, which is the most cost-effective medication for the treatment of iron deficiency anemia. The optimal response can be achieved with a dosage of 3 to 6 mg/kg of elemental iron per day. Parenteral iron therapy or red blood cell transfusion is usually not necessary.

***Conclusion*:** In spite of a decline in prevalence, iron deficiency anemia remains a common cause of anemia in young children and adolescents, especially in developing countries; hence, its prevention is important. Primary prevention can be achieved by supplementary iron or iron fortification of staple foods. The importance of dietary counseling and nutritional education cannot be overemphasized. Secondary prevention involves screening for, diagnosing, and treating iron deficiency anemia. The American Academy of Pediatrics recommends universal laboratory screening for iron deficiency anemia at approximately one year of age for healthy children. Assessment of risk factors associated with iron deficiency anemia should be performed at this time. Selective laboratory screening should be performed at any age when risk factors for iron deficiency anemia have been identified.

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1. INTRODUCTION

The word “anemia” is derived from the Greek word “anaimia” meaning without blood. Worldwide, iron deficiency anemia is the most prevalent nutritional deficiency disorder and the leading cause of anemia in children, especially in developing countries [1-4]. When present in early childhood, especially if severe and prolonged, iron deficiency anemia can result in neurodevelopmental and cognitive deficits, which may not always be fully reversible even with correction of the iron deficiency anemia [5-7]. In recent years, the prevalence of iron deficiency anemia has declined at least in part due to iron fortification of milk formulas and foods and routine iron supplements for individuals at risk for iron deficiency anemia [8]. Nevertheless, iron deficiency anemia is still prevalent around the world. As such, physicians need to be competent in diagnosing and managing iron deficiency anemia. A review on the topic is, therefore, in order and is the purpose of the present communication.

A PubMed search was completed in February 2023 in Clinical Queries using the key term "iron deficiency anemia". The search strategy included all clinical trials (including open trials, non-randomized controlled trials, and randomized controlled trials), observational studies (including case reports and case series), and reviews (including narrative reviews and meta-analyses) published within the past 10 years. Google, UpToDate, and Wikipedia were also searched to enrich the review. Only papers published in the English literature were included in this review. The information retrieved from the search was used for the compilation of the present article.

2. DEFINITION

Iron deficiency is defined as a health-related condition in which the iron supply is not sufficient to meet the body’s requirements for the maintenance of normal physiologic functions and can be present with or without anemia [9, 10]. Iron deficiency in the pediatric age group is arbitrarily deemed to be present when the serum ferritin level is less than 15 μg/L [11]. Iron deficiency anemia occurs when iron deficiency is severe enough to affect erythropoiesis (evidenced by low serum iron level, low serum ferritin level, low serum transferrin saturation, and reduction of iron stores), leading to the development of anemia. Iron deficiency anemia is defined as a hemoglobin (Hb) concentration that is two standard deviations or more below the mean for a healthy population of the same age and sex with a serum ferritin level less than 15 μg/L [11].

3. IRON METABOLISM

Iron is an essential component of many enzymes involved in multiple metabolic processes (*e.g.*, deoxyribonucleic acid [DNA] replication and repair, adenosine triphosphate [ATP] production, oxygen transport, and electron transport) and adequate functioning of all body cells. The human body contains approximately 35 mg of elemental iron per kg of body weight [12]. Approximately 75% iron is bound in the heme proteins, namely Hb (the most abundant iron-containing protein) and myoglobin [13, 14]. Approximately 3% of iron is bound in critical enzyme systems, such as cytochromes, peroxidases, and catalase [11, 14]. The remaining is stored primarily in the reticuloendothelial cells of the bone marrow, spleen, and liver as ferritin and hemosiderin [14]. Storage iron exists primarily in ferric salt-protein complexes.

Iron, whether dietary or pharmacological, is absorbed primarily in the duodenum and upper jejunum, and is highly regulated by the peptide hormone hepcidin to ensure that sufficient iron is absorbed to compensate for the loss of iron from the body [15]. Hepcidin, synthesized in hepatocytes, is a negative regulator of iron export [16]. Hepcidin binds to ferroportin (a transmembrane protein found on the basolateral surface of enterocytes that exports iron within cells) with resultant internalization and degradation of ferroportin and retention of iron in macrophages [17, 18]. Iron deficiency causes hepcidin to fall, which allows enhanced dietary iron absorption and transport by ferroportin [11]. On the other hand, higher hepcidin levels and decreased iron absorption result when the body’s iron stores are normal or high. On top of this, when the body’s iron stores are high, much of the iron that is taken up by the enterocytes is sloughed into the intestinal lumen by desquamation at the end of their two to three-day lifespan. The iron absorbed in the small intestine is then transported in blood by transferrin to erythroid precursor cells in the bone marrow [15].

Heme and nonheme iron are the two major sources of iron in the diet. Heme iron found in meat, poultry, and fish is highly bioavailable and is two to three times more absorbable than nonheme iron [19, 20]. This is because heme carrier protein 1 (HCP1) facilitates the transport of heme iron into the enterocyte [21]. Within the enterocyte, iron is released from heme-by-heme oxygenase and enters the circulation as nonheme iron (inorganic iron).

Nonheme iron is found in vegetables, eggs, and iron-fortified foods, primarily in the ferric form [22]. In the process of digestion, the iron is reduced from the ferric to the ferrous form *via* the enzyme ferric reductase. The ferrous form is more readily absorbed. The absorption of nonheme iron is enhanced by hydrochloric acid in gastric juice and ascorbic acid [20, 23]. On the other hand, the absorption of nonheme iron is inhibited by polyphenols (in certain vegetables and legumes), tannates (in tea, cereals, peas, and legume seeds), phytates (in plant fiber), oxalates, carbonates, and phosphates (in high concentration in unmodified cow's milk) [20, 23].

The percentage of iron absorbed from a cow milk formula decreases as the concentration of iron in the formula increases, such that approximately 6% of iron is absorbed from a formula containing 6 mg of elemental iron/L, compared to approximately 4% from a formula containing 12 mg of elemental iron/L [13, 23].

4. NUTRITIONAL REQUIREMENT FOR IRON

At birth, term infants have approximately 75 mg of elemental iron per kg of body weight with two-thirds of ele-

mental iron as Hb [13]. Total body iron changes very little during the first 4 months of life. Although blood volume increases, Hb concentration decreases during this time. Thereafter, approximately 1 mg of elemental iron must be absorbed each day during childhood to maintain a positive iron balance to support on-going growth [13]. As only approximately 10% of dietary iron is absorbed, a dietary intake of approximately 10 mg of iron daily is necessary for optimal nutrition. The National Academy of Medicine (NAM), formerly known as the Institute of Medicine (IOM), recommends dietary intake of elemental iron to be 0.27 mg/day for an infant younger than 6 months of age, 11 mg/day for an infant 6 to 12 months of age, 7 mg/day for a child 1 to 3 years of age, 10 mg/day for a child 4 to 8 years of age, 8 mg/day for a child 9 to 13 years of age, 11 mg/day for a male 14 to 18 years of age, and 15 mg/day for a female 14 to 18 years of age [24]. During pregnancy, the requirement for iron intake goes up to 22 mg/day [25].

5. EPIDEMIOLOGY

The prevalence of iron deficiency anemia varies widely depending on a multitude of factors, such as age, dietary habits, socioeconomic status, ethnic composition, and the criteria used to establish the diagnosis. In general, iron deficiency anemia is most common among children aged nine months to three years [26, 27]. The prevalence drops among school-age children but increases again during adolescence [28]. Risk factors for iron deficiency anemia include maternal iron deficiency, prematurity, low birth weight, small for gestational age, twin pregnancy, twin to twin transfusion, intrauterine growth retardation, immediate clamping of the umbilical cord at birth, perinatal bleeding, use of low-iron infant formula, prolonged breast feeding without iron supplementation, delayed introduction of solid foods after six months, consumption of unmodified cow milk (non-formula cow milk) before one year of age, excessive intake of cow milk in toddlers and young children, lack of iron-rich foods in childhood and adolescence, low socioeconomic status, poverty, high birth order, poor nutritional status, rapid growth (*e.g.*, adolescence), obesity, type 2 diabetes mellitus, lead exposure or poisoning, heavy menstrual bleeding, pregnancy, gastrointestinal diseases (*e.g.*, Crohn disease, celiac disease, short bowel syndrome), and children of Black/ Hispanic/Latin American descent (presumably because of diet and socioeconomic factors) [29-39]. In the United States, the prevalence of iron deficiency anemia has declined in the past five decades. In the early 1970s, iron deficiency anemia affected up to 76% of children one to two years of age attending public health clinics [40, 41]. Between 1975 and 1985, the prevalence of iron deficiency anemia in children younger than two years decreased from 8% to 3% [42, 43]. According to the National Health and Nutrition Examination Survey (NHANS) conducted from 2007 to 2010, 1.1% of children aged one to five years and 2.4% of adolescent girls in the United States had iron deficiency anemia [24, 44]. These trends most likely reflect the widespread use of iron-fortified infant formulas and foods. However, minority and immigrant children remain at increased risk for iron deficiency anemia [45].

6. ETIOLOGY

The etiology of iron deficiency anemia varies greatly. Generally, iron deficiency anemia results when the body's iron demands are not met by iron absorption. Iron deficiency anemia can result from increased demand for iron, inadequate iron intake, decreased iron absorption (malabsorption), increased blood loss, and rarely, defective plasma iron transport [46].

6.1. Increased Physiologic Demands

6.1.1. Rapid Growth

Growth is particularly rapid during the first years of life and again during adolescence. Iron deficiency anemia may occur unless there is a corresponding increase in iron consumption during these physiologic growth periods. In a term infant, the infant doubles the body weight at five months of age and triples the birth weight at one year of age with a corresponding increase in blood volume [13]. Iron deficiency anemia may result from hemodilution. In term infants, because of the abundance of iron stores at birth, iron deficiency anemia is uncommon before 6 months of age. Preterm infants, twins, triplets, and quadruplets have lower iron stores at birth. Iron deficiency is magnified in infants born to mothers with iron deficiency and lower iron storage reserves. Because of a more rapid growth rate and rapid expansion of the blood volume in preterm infants and infants of multifetal pregnancy, their iron stores may be depleted by two to three months of age with ensuing iron deficiency anemia as they grow.

A second growth spurt occurs during adolescence, with rapid expansion of blood volume and body mass and increased iron requirement. Iron deficiency anemia may result if the iron intake is not adequately increased to maintain a corresponding increase in iron requirement.

6.1.2. Pregnancy

During pregnancy, approximately 1,200 mg of iron is required from conception to delivery for the expansion of maternal blood volume by approximately 50%, increase in erythrocyte mass by approximately 35%, and diversion of iron to the fetus for erythropoiesis [42, 47, 48]. Diversion of iron to the fetus for erythropoiesis occurs mainly in the third trimester [49]. Utilization of iron increases from approximately 2 mg/day in early pregnancy to approximately 6 mg/day in the third trimester [47]. Failure to meet this need results in iron deficiency anemia. Blood loss at delivery may result in another 150 to 200 mg of iron loss [13]. Although menstruation ceases and iron absorption increases during pregnancy, most pregnant women who do not take iron supplements become anemic. This problem is especially exaggerated with twin or multifetal pregnancy.

6.2. Inadequate Iron Intake

A diet poor in iron is a major contributing factor to the development of iron deficiency anemia [50]. Both breast milk and unmodified cow milk are notoriously poor in iron,

containing less than 0.7 mg/L of elemental iron. Iron in breast milk, however, is highly bioavailable, possibly because of the lower calcium content and the presence of lactoferrin [22]. Approximately 50% of the iron in breast milk is absorbed, in contrast to about 10% of the iron in unmodified cow milk [7]. Nevertheless, prolonged predominant breast-feeding beyond six months of age without iron supplementation may also lead to iron deficiency anemia in approximately 30% of these infants at 12 months of age [51-53]. Iron deficiency anemia may be caused by excessive consumption of cow milk (thereby limiting intake of solid foods) without iron supplementation [54, 55]. Insufficient dietary intake of iron may result from chronic consumption of a vegetarian diet (poor bioavailability of iron in phytate and fiber-rich diet) or restricted diets low in iron. Adolescents face additional challenges. The lack of nutrition knowledge, concern about body image, and food fads often lead to inadequate iron intake and the development of iron deficiency anemia.

6.3. Malabsorption

Malabsorption of iron may result from achlorhydria or hypochlorhydria, extensive gastrointestinal surgery (*e.g.*, subtotal or total gastrectomy, bariatric surgery, bowel resection), tropical sprue, nontropical sprue, giardiasis, celiac disease, inflammatory bowel disease, and autoimmune atrophic gastritis [56-58]. Prolonged use of medications, such as proton pump inhibitors, H_2 antagonists, and nonsteroidal anti-inflammatory drugs, and excessive intake of foods containing polyphenols, tannates, phytates, calcium, oxalates, carbonates, and phosphates, may inhibit iron absorption [25, 28].

A rare form of iron deficiency anemia, known as iron-refractory iron deficiency anemia, is caused by loss-of-function mutations in the transmembrane protease serine 6 (*TMPRSS6*) gene that encodes matriptase-2 (MT-2) [59-61]. MT-2 is a negative regulator of hepcidin synthesis [59-61]. With mutations of the *TMPRSS6* gene located on the long arm of chromosome 22 (22q12.3-13.2), excess hepcidin is produced, thereby resulting in the inhibition of intestinal absorption of iron [62]. Iron-refractory iron deficiency anemia is an autosomal recessive disorder characterized by congenital hypochromic, microcystic anemia, low serum iron, low transferrin saturation, normal to high ferritin, and inappropriately high hepcidin for body iron levels [60-63]. Affected individuals have difficulties absorbing iron from dietary sources and are unresponsive to oral iron supplementation [61]. These individuals are partially responsive to parenteral iron therapy [64].

6.4. Blood Loss

6.4.1. Gastrointestinal

Iron deficiency anemia may develop in children with cow milk protein allergy secondary to gastrointestinal blood loss [65, 66]. Consumption of unmodified cow milk in early infancy increases gastrointestinal blood loss [67]. A heat-labile protein in cow milk, such as lactalbumin, has been postulated to be the cause of gastrointestinal bleeding [67, 68].

Iron deficiency anemia may also result from Meckel diverticulum, peptic ulcer, intestinal polyp, intestinal hemangioma, hereditary hemorrhagic telangiectasia, celiac disease, and inflammatory bowel disease (*e.g.*, Crohn's disease, ulcerative colitis) [69-74].

Infestation with *Ancylostoma duodenale* and *Necator americanus* (hookworms) is an important cause of intestinal blood loss in tropical and subtropical areas [75, 76]. On average, a hookworm survives on approximately 0.4 ml of blood per day extravasated from the intestinal mucosa [42]. Infestation with *Diphyllobothrium latum* (broad or fish tapeworm), *Schistosoma mansoni* (blood fluke), *Ascaris lumbricoides*, *Giardia lamblia*, and *Entamoeba histolytica* is a less common cause of intestinal blood loss [57, 77-79].

Conversely, severe iron deficiency may lead to histologic changes in the intestinal mucosa with resultant occult bleeding. Iron deficiency may also induce enteropathy, or leaky gut syndrome, further aggravating the anemia [41].

6.4.2. Genitourinary

Menstruation, especially menorrhagia, is a common and important cause of iron deficiency anemia in adolescent girls as the iron demand is high in menstruating females [80, 81]. The average menstrual blood loss is about 40 mL (15 g of Hb/mL), resulting in 20 mg iron loss per period. However, in 10% of females, menstrual blood loss may exceed 80 mL per period [82]. At times, menorrhagia is severe enough to necessitate urgent medical care, such as emergency department visits and hospitalization [80]. The use of an intrauterine device further increases menstrual blood loss [83].

Hemoglobinuria, an uncommon cause of iron deficiency anemia, may be secondary to glomerulonephritis, paroxysmal nocturnal hemoglobinuria, or intravascular hemolysis associated with prosthetic heart valve replacement (rare nowadays with better prosthesis) [13, 28]. Rarely, iron deficiency anemia may result from hematuria.

6.4.3. Pulmonary

Hemoptysis, an uncommon cause of iron deficiency anemia, can be seen in children with Goodpasture syndrome (characterized by the triad of hemoptysis, diffuse pulmonary infiltrates, and iron deficiency anemia) or idiopathic pulmonary hemosiderosis [13, 84]. Recurrent bleeding into the alveoli can eventually produce pulmonary hemosiderosis and fibrosis. Since the iron released and stored by pulmonary macrophages is isolated from the circulation, iron trapped within these pulmonary macrophage cells is unavailable for the synthesis of Hb by erythroblasts in the bone marrow [13].

6.4.4. Cutaneous

Iron deficiency anemia may result from frequent epistaxis and chronic pediculosis or bed bug infestation [85, 86].

6.4.5. Iatrogenic

Iron deficiency anemia may result from frequent phlebotomies, surgical losses, or excessive blood donations. Patients undergoing hemodialysis are particularly at risk because of blood loss into the dialysis machine and tubing, regular blood sampling, and occult bleeding from the gastrointestinal tract [87]. Early clamping of the umbilical cord reduces the newborn's iron content by 15% to 30% [88, 89].

6.4.6. Perinatal Hemorrhage

Iron deficiency anemia may be secondary to perinatal hemorrhage, such as fetal-maternal transfusion, fetal-to-fetal transfusion, and bleeding from the placenta.

6.5. Defective Plasma Iron Transport

Iron deficiency anemia may, very rarely, result from congenital atransferrinemia [90, 91]. Congenital atransferrinemia is characterized by early onset of moderate to severe iron deficiency, undetectable serum transferrin (TF), high serum ferritin, and excess iron stored in peripheral tissues (secondary hemochromatosis) [92, 93]. The condition is inherited as an autosomal recessive disorder due to a mutation in the *TF* gene located on chromosome 3q21 [93]. The gene encodes TF, a glycoprotein with a single polypeptide chain with a molecular weight of approximately 90,000 Daltons [93, 94]. TF, the main serum iron transporter synthesized predominately in the liver, takes up iron from the intestinal enterocytes and delivers iron to erythroid precursors in the bone marrow for Hb synthesis [95, 96]. In congenital atransferrinemia, the iron that is absorbed is either free in circulation or loosely bound to other plasma proteins. Much of the iron is taken up by the liver because such uptake is not mediated by TF [13]. However, the uptake of iron by erythroid precursors in the bone marrow is insufficient because such a process is mediated by TF.

6.6. Miscellaneous

There is considerable evidence that persistent *Helicobacter pylori* infection is associated with iron deficiency anemia in children (particularly, adolescents) and adults [97, 98]. Pathogenetic mechanisms due to which *H. pylori* infection can lead to iron deficiency anemia include impaired iron absorption due to hypochlorhydria resulting from *H. pylori* gastritis (particularly, atrophic gastritis), increased serum hepcidin, competitive binding with iron between *H. pylori* and humans, use of proton pump inhibitors in the treatment of *H. pylori* gastritis, and blood loss from gastritis and peptic ulceration (rare in children) [97, 99, 100]. A systematic review and meta-analysis of 14 observation studies that addressed the association between *H. pylori* infection and iron deficiency anemia showed an increased likelihood of iron deficiency anemia among *H. pylori* individuals (pooled odds ratio: 1.33; 95% confidence interval: 1.23 to 2.42) [101].

7. CLINICAL MANIFESTATIONS

The symptoms and signs of iron deficiency anemia are varied and often non-specific. The prominence of the symptoms and signs depends on both the degree and the rate of development of the anemia. The majority of children with mild iron deficiency anemia are asymptomatic [14]. Pallor is the most frequent presenting feature and is best detected at the conjunctivae, nail beds, and palms. In mild to moderate iron deficiency anemia, poor appetite, easy fatigability, lassitude, lethargy, exercise intolerance, weakness, irritability, and dizziness may be seen [102]. In severe iron deficiency anemia, tachycardia, shortness of breath, diaphoresis, poor capillary refilling, soft ejection systolic flow murmurs, and cardiomegaly may occur [42, 103]. Because anemia is often insidious, adaptive circulatory and respiratory responses may minimize these manifestations [19]. Children can often tolerate Hb concentrations of 30 to 40 g/L with remarkably few symptoms, unless an intercurrent infection triggers tachycardia and cardiac decompensation. The spleen is palpable in 10% to 15% of patients [13]. Rarely, pseudotumor cerebri (papilledema, increased intracranial pressure), retinal hemorrhages, and retinal exudates may be seen in patients with severe iron deficiency anemia [104]. In chronic severe iron deficiency, blue sclerae (caused by impairment of collagen synthesis with resultant thinning of the sclerae), angular cheilitis, glossitis with atrophy of the lingual papillae rendering the tongue a glossy appearance, spoon-shaped nails (koilonychia) (Fig. **1**), and widening of the diploe of the skull, may occur [19, 25, 105]. The latter is due to an expansion of the medullary space by the bone marrow.

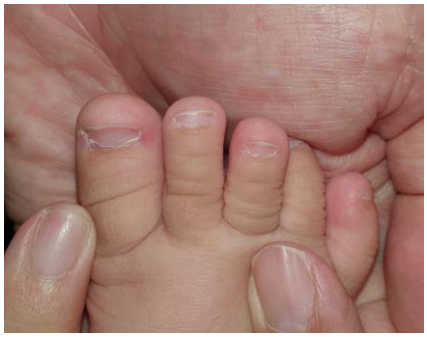

Fig. (1). Spoon-shaped toenails seen in a 3-year-old child with iron deficiency anemia. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

8. CONDITIONS AND COMPLICATIONS ASSOCIATED WITH IRON DEFICIENCY/IRON DEFICIENCY ANEMIA

Conditions and complications associated with iron deficiency with or without anemia include cold intolerance, tingling, numbness, gastric atrophy, and post-cricoid esophageal web or stricture presumably caused by intracellular iron deficiency [106]. A rare complication of iron deficiency is Plummer-Vinson syndrome, which is characterized by the triad of iron deficiency anemia, progressive dysphagia, and acquired upper esophageal webbing [107, 108].

Iron plays an essential role in the myelination of the white matter of the central nervous system and the spinal cord, the production and functioning of neurotransmitters, such as aldehyde oxidase, dopamine, serotonin, norepinephrine, and monoamine oxidase, as well as brain development

[78, 109]. Oligodendrocytes that produce myelin require iron for maturation and function [110]. Zheng *et al*. assessed the neurobehavioral development (gross motor, fine movement, language, social behavior, and adaptability) of 711 children 6 to 21 months of age with iron deficiency anemia seen at the Maternal and Child Health Hospital in Guangzhou, China between January 1, 2018, and December 31, 2019 [111]. The authors found that children with iron deficiency anemia had a significantly lower development quotient for total neurobehavioral development than those children without anemia [111]. The partial regression coefficients were -1.33 (95% confidence interval: -2.36 to -0.29; $p = 0.012$). The severity, early onset, and prolonged duration of iron deficiency anemia correlate with poorer performance [13]. As infancy is the critical period for brain development, severe, chronic iron deficiency anemia in early childhood (especially in infancy) is associated with impaired psychomotor and cognitive development, which may be long-lasting [112-122]. In some studies, improvement in psychomotor and cognitive development has been noted with iron therapy [15, 117, 118, 123, 124]. Further studies are necessary to determine the effects of the chronicity, severity, and age of onset of iron deficiency anemia, as well as the duration of treatment, on the reversibility of cognitive function later in life.

Children with iron deficiency anemia are at increased risk for sensorineural hearing loss [125-128]. It is postulated that sensorineural hearing loss may result from impaired myelination of the auditory brainstem and compromised oxygen/blood supply to the inner ears as a result of iron deficiency anemia [126-128]. In a study of 20,113 patients (aged 4 to 21 years) seen at the Penn State Milton S. Hershey Medical Center in Hersey, Pennsylvania, who were examined for hearing loss and iron deficiency anemia. The prevalence of iron deficiency anemia and sensorineural hearing loss was 2.3% and 1.7%, respectively [127]. The prevalence of hearing loss was 3% in the iron deficiency anemia cohort and 1.7% in those patients without iron deficiency anemia [127]. The study showed that patients with iron deficiency anemia are at increased risk for sensorineural hearing loss (odds ratio: 3.67; 95% confidence interval:1.6 to 7.3).

Children with iron deficiency anemia are at increased risk for attention deficit hyperactivity disorder [129-134]. It has been postulated that iron deficiency in the basal ganglia and thalamus leads to abnormal functioning of the dopaminergic system [135-137]. In one study of 2,957 children (mean age: 10.59 ± 6.02 years) with iron deficiency anemia, attention deficit hyperactivity disorder was identified in 84 (2.8%) children *versus* 207 (1.8%) of 11,828 children in the control group (odds ratio: 1.67; 95% confidence interval: 1.29 to 2.17) [135].

Iron deficiency may adversely affect the child's growth through a reduction in the oxygen-carrying capacities of erythrocytes and serum insulin-like growth factor-I (IGF-I) concentrations and erythropoietic activities [138]. Chronic severe iron deficiency in early childhood (especially in the first two years of life) is often associated with a reduction in growth rate [139, 140]. Although both reduced growth rate and iron deficiency may be secondary to an overall nutritional deficiency, several studies have shown that iron supplementation improves the physical growth of children with iron deficiency anemia independent of their nutritional status [140-143].

Exercise and physical work capacity are impaired in individuals with iron deficiency anemia. Studies have shown that affected individuals have reduced muscle strength [144, 145]. The impairments can be attributed to low Hb as well as to a deficiency in iron-containing respiratory enzymes [146-149]. Correction of iron deficiency leads to an improvement in the exercise capacity [150].

The association of pica with iron deficiency or iron deficiency anemia is well documented [151-153]. Geophagia (compulsive eating of dirt) is more common in children with iron deficiency [152]. On the other hand, pagophagia (compulsive craving or chewing of ice) is particularly common in adults with iron deficiency [151-153]. Pica may induce iron deficiency by providing a diet low in iron or by binding iron to the dirt or clay inhibiting the intestinal absorption of iron [152]. There is considerable evidence that iron deficiency is the cause rather than the consequence of pica [154, 155]. Studies have shown that correcting iron deficiency eliminates pica [155-157].

Iron deficiency anemia may contribute to lead poisoning in children by increasing the intestinal absorption of lead [90]. Also, children with pica are at a particular risk of lead poisoning if lead is prevalent in the surrounding environment [158].

Iron deficiency can adversely affect immune functions by causing decreased myeloperoxidase activity, reduced phagocytic activity, reduced bactericidal capacity, a quantitative decrease in the number of circulating T-cells, lower immunoglobulin G (IgG) levels, impaired interleukin (IL) production (particularly, IL-2, IL-6), impaired mitogenic response, and poor natural killer activity [159-161]. It can be argued that recurrent infections may impair iron absorption and predispose to iron deficiency [162]. As such, iron deficiency anemia may be the result rather than the cause of recurrent infections. The relation is further confounded by socioeconomic and environmental variables that may predispose the child to both infection and iron deficiency anemia [139]. In a birth cohort study involving 303 Kenyan infants followed from birth to 18 months of age, iron deficiency anemia at the time of vaccination decreased vaccine response and iron supplementation increased humoral vaccine response [163]. Further studies are necessary to confirm or refute these findings.

Iron is essential for cerebral neurotransmission. There is considerable evidence that iron deficiency and, in particular, iron deficiency anemia plays an essential role in the initiation of breath-holding spells [164-169]. Studies have shown that treatment of iron deficiency anemia with iron supplementation often results in improvement or resolution of breath-holding spells [170-173].

Children with iron deficiency anemia have an increased risk of febrile seizures [174-185]. Iron deficiency anemia may predispose to febrile seizures by lowering the release of

neurotransmitters, such as aldehyde oxidase and monoamine oxidase, thereby lowering the seizure threshold [174, 175]. A 2017 meta-analysis of 17 studies (2,416 children with febrile seizures and 2,387 children without febrile seizures as controls) showed iron deficiency as significantly associated with febrile seizures (odds ratio: 1.98; 95% confidence interval: 1.26 to 3.13; $p = 0.003$) [186].

Iron deficiency anemia has, rarely, been reported to be associated with stroke in children [187-195]. Children with iron deficiency anemia tend to be at higher risk for thrombosis [191-193]. It has been postulated that stroke may be caused by cerebral vein thrombosis secondary to reactive thrombocytosis, increased procoagulants, increased platelet aggregation, microcytosis, turbulent blood flow, alterations in laminar flow, rigidity/reduced deformability of erythrocytosis, and anemic hypoxia [187-189]. In a case-control study (15 children aged 12 to 38 months with stroke; 143 healthy children matched for age and sex), conducted at the Hospital for Sick Children in Toronto, Canada, it was found that previously healthy children with stroke were 10 times more likely to have iron deficiency anemia than healthy children without stroke [192].

Subclinical renal injury may result from iron deficiency anemia [196, 197]. Preliminary studies have shown that urinary kidney injury markers, including kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), and liver-type fatty acid-binding protein (L-FABP), are increased in children with iron deficiency anemia [196, 197].

Iron deficiency anemia may exacerbate an underlying chronic disease, leading to higher mortality and morbidity [10]. In chronic severe iron deficiency, intestinal function may be impaired resulting in malabsorption of nutrients, protein-losing enteropathy, or leaky gut syndrome [198].

Pregnant women suffering from iron deficiency anemia are at increased risk of preterm delivery, small for gestational age, perinatal mortality, and maternal mortality [199-201]. In one study, the odds of preterm delivery were increased 5-fold for iron deficiency anemia and doubled for other anemias [202].

9. LABORATORY FEATURES

In iron deficiency anemia, a peripheral blood smear typically shows microcytosis and hypochromia with substantial anisocytosis (Fig. **2**) [7, 203]. Elliptocytic (cigar-shaped) erythrocytes are often seen in iron deficiency anemia.

A complete blood count shows that the Hb, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), absolute reticulocyte count, and reticulocyte Hb content are lower than normal in patients with iron deficiency anemia, [204, 205]. The red blood cell distribution width (RDW) is a measure of anisocytosis (variability in erythrocyte size), which is the earliest recognizable hematologic manifestation of iron deficiency [7, 203, 206]. An RDW greater than 14% is always seen in iron deficiency [7, 203, 206]. In this regard, a rise in absolute reticulocyte count and reticulocyte Hb content is the earliest indicator of response to iron therapy [13]. The white blood cell (WBC) count is usually normal. The platelet count is normal or increased. Thrombocytopenia is relatively rare.

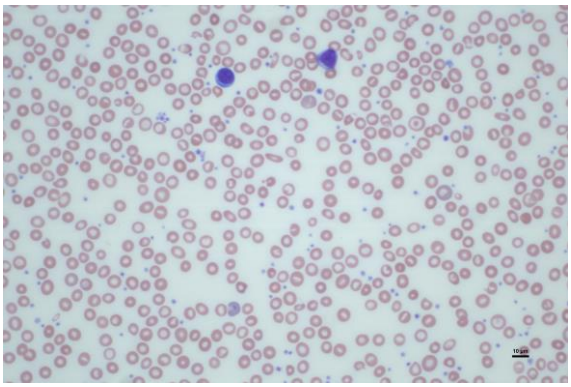

Fig. (2). Peripheral blood smear of a 15-year-old girl with iron deficiency anemia due to duodenal ulcer, featuring hypochromic microcytic red cells with anisocytosis and occasional elliptocytes. Mild thrombocytosis is appreciated. Two lymphocytes are shown for comparison of red cell size (original magnification x 400). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

A serum ferritin level between 10 and 20 μg/L indicates depletion of iron stores, whereas a serum ferritin level less than 10 μg/L is diagnostic of iron deficiency. The serum ferritin level may be elevated in the presence of inflammation, infection, malignancy, or hepatic disease [19]. Therefore, a normal or mildly elevated serum ferritin level can be seen in patients with iron deficiency. However, a serum ferritin level greater than 50 μg/L generally excludes iron deficiency anemia [207].

Serum iron levels are less useful in the diagnosis of iron deficiency anemia as low serum iron levels can also be seen in the presence of inflammation or malignancy. A total iron-binding capacity (TIBC) greater than 400 μg/dL (normal: 200 to 400 μg/dL) suggests iron deficiency, whereas a value less than 200 μg/dL is characteristic of an inflammatory disease [207]. TF saturation (TSAT) less than 7% is consistent with iron deficiency [207]. The serum TF receptor level is elevated in iron deficiency anemia [15]. The level of free erythrocyte protoporphyrin (FEP), a heme precursor, is increased (greater than 3 μg/g of Hb) in disorders of heme synthesis, such as iron deficiency, lead poisoning, and sideroblastic anemia [208]. A low serum hepcidin level is seen in children with iron deficiency anemia [209].

10. DIAGNOSIS

Anemia caused by iron deficiency should be suspected if there is a history of poor dietary intake of iron, a history of excessive blood loss, and pallor on physical examination. If iron deficiency appears likely on clinical grounds, a low Hb and a peripheral blood smear showing hypochromia, microcytosis, and elliptocytosis are sufficient to make the diagnosis of iron deficiency anemia, although a low serum ferritin

level will provide additional valuable information. Alternatively, an empiric therapeutic trial of oral iron therapy may be considered without further testing in the absence of reticulocytosis and splenomegaly. A therapeutic trial consists of oral supplementation of 3 mg/kg of elemental iron once a day as ferrous sulfate between meals for four weeks [7]. Milk should be avoided for approximately an hour before and two hours after the oral dose of iron therapy [11]. A rise in the Hb concentration of 10 g/L or more after four weeks of iron therapy is generally considered diagnostic of iron deficiency anemia [7].

When the diagnosis of iron deficiency anemia is in doubt, more extensive laboratory testing is appropriate. The most common parameters for diagnosing iron deficiency anemia include decreased Hb, decreased MCV, decreased MCH, increased RDW, and increased FEP levels. A serum ferritin level of less than 15 μg/L or a TSAT of less than 7% confirm the diagnosis of iron deficiency anemia in the majority of cases.

11. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypochromic microcytic anemia includes thalassemia, including β thalassemia trait and α thalassemia trait, anemia seen in lead poisoning, anemia of chronic disease/inflammation, and sideroblastic anemia [208]. Both thalassemic traits and iron deficiency anemia produce hypochromic microcytic anemia. In both the β thalassemia trait and the α thalassemia trait, the anemia is usually mild, but microcytosis and hypochromia are prominent and out of proportion to the degree of anemia. Also, in some cases of thalassemia traits, target cells and basophilic stippling are seen in the peripheral blood smear [210]. In contrast to children with iron deficiency anemia, children with thalassemia traits have normal red blood cell count, serum ferritin level, TSAT, and FEP level [13]. The RDW and RDW index (a more sensitive and precise test) are higher in children with iron deficiency anemia than in children with thalassemia traits [207, 211]. On the other hand, the microcytic to hypochromic ratio is higher in children with thalassemia traits compared to children with iron deficiency anemia [210, 212]. On top of these, many indices, such as the Mentzer index, Shine and Lal index, Srivastava index, England and Fraser index, and Green and King index, have been used to discriminate thalassemia traits from iron deficiency anemia *via* parameters obtained from automated blood cell analyzers with variable sensitivities and specificities [213]. Confirmatory tests include high-performance liquid chromatography, HbH bodies detection, Hb electrophoresis, and DNA studies. On high-performance liquid chromatography, HbA_2 and sometimes Hb F are elevated in children with β-thalassemia trait. Occasional HbH bodies can be found in many children with alpha thalassaemia trait.

Children with lead poisoning are often asymptomatic. When symptoms occur, they are nonspecific and include headache, anorexia, abdominal pain, and constipation [214-217]. With chronic lead poisoning, symptoms include agitation, growth retardation, developmental delay, ataxia, clumsiness, hyperirritability, short attention span, hyperactivity, increased antisocial behavior, somnolence, stupor, and seizures [214-218]. In prolonged and severe lead poisoning, a blue-purplish line (lead line or Burton line) may be seen at the junction of the teeth and gum [215, 219], and peripheral blood smear typically shows hypochromia, microcytosis, and coarse basophilic stippling [220, 221]. In lead poisoning, there is an elevated blood lead level and marked elevation of FEP (>18 μg/g of Hb) [13].

The anemia of chronic disease/inflammation results from an inflammation-induced block in intestinal absorption of iron and retention of iron in the reticuloendothelial cells [222]. Diseases that most often lead to anemia of chronic disease/inflammation include chronic infection (*e.g.*, tuberculosis, human immunodeficiency virus [HIV] infection), autoimmune diseases (*e.g.*, systemic lupus erythematosus, rheumatoid arthritis), immunodeficiency, renal failure, and malignancy [223]. Although decreased Hb level, decreased red blood cell count, decreased serum iron, and increased FEP can be found in both iron deficiency anemia and anemia of chronic disease/inflammation, the anemia of chronic disease/inflammation is associated with normal MCV/MCH (decrease in iron deficiency anemia), increased serum ferritin (low in iron deficiency anemia), decreased TIBC (increase in iron deficiency anemia), normal RDW (increase in iron deficiency anemia), normal reticulocyte Hb content (low in iron deficiency anemia), high serum hepcidin concentration (low in iron deficiency anemia), increase in C-reactive protein (normal in iron deficiency anemia), decreased serum folic acid concentration (normal in iron deficiency anemia), decreased serum vitamin B_{12} concentration (normal in iron deficiency anemia), and decreased serum erythropoietin concentration (increase in iron deficiency anemia) [222, 223].

Sideroblastic anemia, resulting from ineffective erythropoiesis with iron overload, can be congenital or acquired [224]. The anemia can be hypochromic, microcytic (most common), normocytic, or macrocytic [225]. Complete blood count shows a low Hb, normal red cell count, low MCV, low MCH, and high RDW [224]. Serum ferritin and TSAT are typically elevated [224]. In severe and chronic cases, the peripheral blood smear often shows target cells, poikilocytosis, anisocytosis, and occasional siderocytes. The presence of ring sideroblasts in a bone marrow aspirate using Prussian blue stain is diagnostic [224-226]. Ring sideroblasts are erythroblasts containing coarse sideroblastic (non-heme iron) granules in mitochondria surrounding the nucleus [226].

12. MANAGEMENT

Treatment of iron deficiency anemia consists of replenishing iron stores, restoring Hb concentrations to normal levels, and correcting the underlying etiology. Oral iron therapy remains the first-line approach for the treatment of iron deficiency anemia [227]. This can be achieved by the oral administration of a ferrous salt, which is the most cost-effective medication for the treatment of iron deficiency anemia [227]. The absorption of ferrous salts is about three times better than that of ferric salts [228]. Ferrous sulfate is

usually preferred because of its efficacy, low cost, better absorption, high bioavailability, tolerability, and less adverse events associated with its use [228, 229]. Ferrous sulfate is 20% elemental iron by weight. Optimal response (an increase in reticulocyte is seen in approximately 72 hours) is achieved with a dosage of elemental iron of 3 to 6 mg/kg per day (3 mg/kg of elemental iron administered once daily; a higher dose of elemental iron requires administration in 2 to 3 divided doses) [38, 230]. The dose given depends on the severity of iron deficiency anemia. In general, a dose higher than 6 mg/kg per day does not offer an extra advantage [231]. Other oral iron formulations that have proven efficacy in the treatment of iron deficiency anemia include ferrous gluconate, ferrous fumarate, iron polymaltose complex (consisting of ferric hydroxide and polymaltose), polysaccharide-iron complex, heme iron polypeptide, carbonyl iron, and multivitamin plus iron [232-239]. For best absorption, iron should be given between meals with fruit juice (ascorbic acid facilitates iron absorption), but not with milk [230]. Gray staining of teeth may occur with liquid iron preparations and is often temporary [14]. Staining of the teeth can be minimized by placing the medication with a dropper or syringe toward the back of the mouth and/or rinsing the mouth with water or brushing the teeth after administration of liquid iron preparations [14]. Other adverse events are uncommon and are dose-related. These adverse events include nausea, epigastric/abdominal discomfort/pain, constipation, and diarrhea [207, 230]. Reducing the dosage of the medication or giving it with food minimizes these side effects. To increase intestinal absorption, iron preparations should be given between meals with vitamin C-containing juice. Oral iron therapy should be given for at least three months and at least one month after the Hb level is within the normal range to restore iron stores [230].

Failure to respond to oral iron therapy may be caused by poor compliance, an inadequate iron dose, an ineffective iron preparation, ongoing blood loss, coexistent disease that interferes with absorption or utilization of iron, iron-refractory iron deficiency anemia, or an incorrect diagnosis (*e.g.*, thalassemia trait, anemia of chronic disease) [14, 15].

The use of parenteral (intramuscular or intravenous) iron therapy instead of oral iron therapy will not increase the rate of response. Although the initial rise in Hb tends to be faster with parenteral iron therapy, the rise in Hb is similar to oral iron therapy at about the sixth week of treatment [12]. In addition, parenteral iron therapy is expensive and has greater morbidity than oral iron therapy, and therefore should be avoided if possible. Intravenous iron therapy should be reserved for patients with persistent or severe iron deficiency anemia who have proven intolerance to oral iron therapy, have malabsorption of iron (*e.g.*, celiac disease, inflammatory bowel disease), nonadherence to oral iron therapy, are refractory to oral iron therapy despite good adherence to treatment, have ongoing iron losses exceeding maximal oral replacement, and those with chronic renal failure undergoing hemodialysis who are treated with erythropoietin [12, 207, 227, 230, 240, 241]. Intravenous iron formulations that have demonstrated efficacy in the treatment of iron deficiency anemia include iron sucrose, ferric gluconate, ferric carboxymaltose, ferumoxytol, and low-molecular-weight iron dextran [242-256]. High-molecular-weight iron dextran should not be used because of its higher risks of adverse events, and it has also been withdrawn from many countries [240]. In general, intravenous iron therapy is safe [240, 256-258]. Adverse events associated with intravenous infusion of iron include anaphylaxis (the most feared adverse event), shivering, hypotension, shock, fever, headache, flushing, malaise, nausea, vomiting, abdominal pain, urticaria, myalgia, arthralgia, lymphadenopathy, and pleural effusion [207, 230]. Intramuscular injection of iron is painful and may be associated with permanent brown staining of the skin and subcutaneous tissues, muscle necrosis, atrophy, fibrosis, and sterile abscesses [12].

Red blood cell transfusions are rarely required and should be reserved for patients with very severe anemia, especially those with significant acute bleeding. Packed red blood cell transfusion should be administered slowly in an amount sufficient to raise the Hb to a safe level (about 70 g/L), at which the response to iron therapy can be awaited [13]. Children with impending cardiac decompensation (usually precipitated by a fever of an intercurrent infection) may be best managed by a partial exchange transfusion with fresh red blood cells [13].

13. PREVENTION

Primary prevention can be achieved by iron supplements or iron fortification of staple foods. The Committee on Nutrition of the American Academy of Pediatrics (AAP) recommends that iron supplementation for all exclusively breast-fed term infants should begin at four months of age and two weeks of age for preterm infants, and continue till appropriate iron-containing complementary foods are introduced into the diet [11, 24, 259]. The dosage of elemental iron is 1 mg/kg per day for term infants. The elemental iron requirements for preterm infants are 2 mg/kg per day and 4 mg/kg per day for infants with birth weights between 1500 and 2500 g, and infants whose birth weights are less than 1500 g at birth, respectively. Iron drops and iron-fortified cereals are good sources of iron. Infants who are partially breast-fed or formula-fed should be given an iron-fortified formula (containing $\geq$ 10 mg/dL of iron) from birth to 12 months of age [24].

Unmodified cow milk should be avoided before 12 months of age [260, 261]. In addition to being a poor source of iron, unmodified cow milk may induce occult gastrointestinal blood loss that may contribute to the development of iron deficiency anemia [260-263]. Children beyond one year of age should limit the intake of unmodified cow milk to no more than 500 ml per day [24].

Children should have enough dietary intake of iron through iron supplements or fortification of foods to maintain a positive iron balance to support ongoing growth [264]. The importance of dietary counseling and nutritional education cannot be overemphasized. Iron-rich complementary foods should be started no later than six months of age [11].

The daily elemental iron requirement is as follows: 7 mg/day for a child 1 to 3 years of age, 10 mg/day for a child 4 to 8 years of age, 8 mg/day for a child 9 to 13 years of age, 11 mg/day for a male 14 to 18 years of age, and 15 mg/day for a female 14 to 18 years of age [24]. A meta-analysis of six studies (n = 676) showed dietary interventions, such as fortification of foods, are effective in improving iron deficiency in children (odds ratio: 5.03; 95% confidence interval: 3.09 to 8.18) [265]. As such, dietary interventions should be part of the overall strategy for the prevention of iron deficiency anemia in children.

Other primary preventative measures include poverty reduction, improvements in antenatal services, delayed clamping of the umbilical cord until one to three minutes after birth, ensuring food security, consumption of iron-rich foods (*e.g.*, red meat, iron-fortified cereals), consumption of foods rich in vitamin C (*e.g.*, fruit, dark green vegetables) at least one feeding per day after a meal, avoidance of foods that reduce absorption of iron (*e.g.*, phytates), and avoidance of taking calcium and iron supplements at the same time as calcium inhibits iron absorption by about 60% [14, 46, 128].

Secondary prevention involves screening for, diagnosing, and treating iron deficiency anemia [20]. Children whose diet contains less than five servings each of meat, fruit, vegetables, and grains per week; daily intake of sweets, fatty snacks, or more than 16 oz of soft drink; or daily intake of more than 16 oz of cow milk, are at risk of iron deficiency anemia [266]. The AAP recommends universal laboratory screening for iron deficiency anemia at approximately one year of age for otherwise healthy children [24]. At the same time, an assessment of risk factors associated with iron deficiency anemia should be performed [24]. Selective laboratory screening should be performed at any age when risk factors for iron deficiency anemia have been identified [227]. Screening for anemia should be considered before six months of age for preterm and low birth weight infants who are not fed an iron-fortified infant formula. For children in the community at high risk for iron deficiency anemia, screening should be performed between 9 and 12 months of age, at 18 months of age, and annually between 2 to 5 years of age [20]. Measurement of Hb, MCV, and RDW is the preferred laboratory test for screening for anemia [24]. If anemia is present, serum ferritin level can be determined to confirm the presence of iron deficiency anemia.

14. PROGNOSIS

The prognosis is generally excellent as most patients with iron deficiency anemia respond favorably to oral iron therapy. The underlying cause should be treated if possible. Patients with proven intolerance to oral iron therapy, iron malabsorption, noncompliance with oral iron therapy, or iron-refractory iron deficiency anemia do not usually respond to oral iron therapy and may require intravenous iron therapy.

CONCLUSION

Worldwide, iron deficiency anemia is the most common hematologic disease in the pediatric age group and a widespread public health problem, especially in developing countries. If not adequately treated, iron deficiency anemia, especially in early life, may lead to neurocognitive impairments, which may be long-lasting. Most patients respond well to oral iron therapy. Iron fortification of milk formulas and staple foods in recent years has reduced the prevalence of iron deficiency anemia in children. Despite this, iron deficiency anemia is still prevalent around the world, especially in developing countries. The importance of dietary counseling and nutritional education cannot be overemphasized.

AUTHORS' CONTRIBUTIONS

Professor Alexander K.C. Leung is the principal author. Dr. Joseph M. Lam, Dr. Alex H.C. Wong, Professor Kam Lun Hon, and Dr. Xiuling Li are co-authors. All the authors have contributed to the drafting and revision of the manuscript, and have approved the final version submitted for publication.

LIST OF ABBREVIATIONS

AAP	=	American Academy of Pediatrics
ATP	=	Adenosine Triphosphate
DNA	=	Deoxyribonucleic Acid
FEP	=	Free Erythrocyte Protoporphyrin
Hb	=	Hemoglobin
HCP1	=	Heme Carrier Protein 1
Hct	=	Hematocrit
IGF-I	=	Insulin-like Growth Factor-I
IgG	=	Immunoglobulin G
IL	=	Interleukin
IOM	=	Institute of Medicine
KIM	=	Kidney Injury Molecule
L-FABP	=	Liver-type Fatty Acid-binding Protein
MCH	=	Mean Corpuscular Hb
MCHC	=	Mean Corpuscular Hb Concentration
MCV	=	Mean Corpuscular Volume
MT-2	=	Matriptase-2
NAG	=	N-acetyl-β-D-glucosaminidase
NAM	=	National Academy of Medicine
NGAL	=	Neutrophil Gelatinase-associated Lipocalin
NHANS	=	National Health and Nutrition Examination Survey
RDW	=	Red Blood Cell Distribution Width
TF	=	Transferrin
TMPRSS6	=	Transmembrane Protease Serine 6
TSAT	=	TF Saturation
WBC	=	White Blood Cell

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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