REVIEW

Diagnosis and Management of Iron Deficiency Anaemia in Children — A Clinical Update

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ABSTRACT

Iron deficiency anaemia (IDA) remains an important public health problem even in developed countries like Singapore. This clinical update covers recent developments in the knowledge of iron metabolism, which aids in the approach towards the diagnosis, management and prevention of IDA in children. Besides IDA, iron deficiency (ID) has several non-haematological consequences including effects on neurocognition and immune function as suggested by several animal and clinical studies. Thus paediatricians and other health care providers should work towards the prevention and elimination of IDA in children.

Keywords: Children, Iron deficiency, Iron deficiency anaemia

INTRODUCTION

IDA remains an important public health problem even in developed countries, especially among toddlers and females of childbearing age[1]. It is the most common and widespread nutritional disorder in the world. There are currently no local statistics on the prevalence of IDA, but studies conducted in other developed countries show that the prevalence of IDA has been estimated to be around 7%–12% in infants[2]. The health consequences of IDA are not trivial and are attributable to the presence of anaemia. Other important consequences include possible neurodevelopmental effects in children and diminished work and productivity in adults with IDA.

DEFINITIONS, CAUSES, AND IMPLICATIONS OF IDA

The World Health Organisation defines anaemia as a haemoglobin (Hb) concentration two standard deviations below the mean Hb concentration for a normal population of the same gender and age range[1]. ID is a state in which there is insufficient iron to maintain normal physiological functions and can result from insufficient intake or excessive losses of iron. The earliest stage of iron depletion starts with diminished iron stores without anaemia while IDA represents the most severe end of the spectrum of ID.

Children are at risk of IDA during periods of rapid growth and erythroid expansion, especially in premature neonates, toddlers, preschool children and adolescents. The most common presentation of IDA is an otherwise asymptomatic, well-nourished infant or child who has a mild to moderate microcytic, hypochromic anaemia. Much less frequent are children with severe IDA, who present with lethargy, pallor, irritability, glossitis, poor exercise tolerance, cardiomegaly, poor feeding, and tachypnea. Pica, which is a bizarre behavioural symptom highly characteristic of severe ID, can develop. Pica is characterised by the inappropriate consumption of non-nutritive substances and it disappears with iron treatment[3]. Severe, long-standing ID may also be associated with koilonychia and the Plummer-Vinson syndrome, but these conditions are very rare in clinical practice in Singapore.

Although IDA is usually due to nutritional insufficiency of iron, it may also be caused by an underlying medical problem such as gastrointestinal blood loss, malabsorption

syndrome, chronic inflammatory disease or heavy menstrual losses. Infants less than 12 months of age who are fed exclusively cow's milk instead of breastmilk or iron-fortified formula milk are at high risk of developing IDA due to the poor iron content of cow's milk and the risk of gastrointestinal bleeding from cow's milk protein allergy.

Besides IDA, several important non-haematological consequences of ID have been implicated in studies:

Neurocognitive Effects

Iron is essential for normal neurodevelopment in a number of animal models, including neuronal energy metabolism, the metabolism of neurotransmitters, myelination, and memory function[4,5]. These observations may explain the behavioural findings in human infants that have been associated with ID. However, important differences exist between animals and humans that must be taken into account in evaluating the implications of results for humans. Randomised trials in infants and toddlers have shown that iron supplementation can prevent or correct impairments in psychomotor development[6-10] but other studies suggest that psychomotor development may not completely recover in children with moderate to severe IDA even after correction of ID[8,11,12].

A Cochrane systematic review conducted by Martins, Logan and Gilbert[13] sought to determine the effects of iron therapy on psychomotor development and cognitive function in iron-deficient children less than three years of age. Studies included children who fulfilled the inclusion criteria and were randomly allocated to iron or iron plus vitamin C versus a placebo or vitamin C alone, and assessments of developmental status or cognitive function were carried out using standardised tests by observers blind to treatment allocation. Five trials involving a total of 180 children with IDA examined the short-term effects of iron therapy on measures of psychomotor development between 5–11 days of commencement of therapy. Data from four trials could be pooled. The pooled difference in pre- to post-treatment change in Bayley Scale Psychomotor Development Index (PDI) between iron-treated and placebo groups was -3.2 (95% CI -7.24 to 0.85) and in Bayley Scale Mental Development Index (MDI) 0.55 (95% CI -2.84 to 1.75). Two other studies looked at the long-term effects of iron replacement therapy by examining its effects on measures of psychomotor development more than 30 days after commencement of therapy. Aukett et. al.[14] reported the mean number of skills gained after two months of iron therapy using the Denver test. The intervention group of 54 children with IDA gained 0.8 (95% CI -0.18 to 1.78) more skills on average than the control group. Idjrandinata et. al.[9] reported a dramatic difference in pre- to post-treatment change between 25 children with IDA treated with iron and 25 children with IDA as placebo after four months using the Bayley Scale PDI of 18.4 (95% CI 10.16 to 26.64) and in Bayley Scale MDI of 18.80 (95% CI 10.19 to 27.41). There is no convincing evidence that iron treatment of young children with IDA has an effect on psychomotor development discernable within 5–11 days although it may take a longer period of time to develop the skills detectable by Bayley scales. The effect of long-term treatment also remains unclear with one study showing no benefit while the other showing a significant improvement in developmental scores. However, the Denver test is not sensitive to small differences and was intended to screen for children with abnormal development and most studies have indicated that the development of children with IDA is normal.

Another widely cited longitudinal observational study was conducted by Lozoff et al[4], who followed 185 Costa Rican children from infancy to 19 years of age. The group with chronic ID in infancy did not catch up with the group with good iron status in standardised cognitive scores over time. Although this study provides important evidence of irreversible neurocognitive consequences in the long-term, it cannot be considered definitive because it was not a double blind, randomised, placebo-controlled trial and did not have a placebo control group.

Interpretation of the relationship between IDA and neurocognition remains limited, not only by potential confounding due to unaccounted nutritional and socioeconomic factors, but by the potential confounding factor of anaemia that accompanies the ID of IDA.

Immunity and infection

The role of iron in immune function remains controversial. Data suggests that ID can be associated with the impairment of cell mediated immunity and the bactericidal activity of

neutrophils, thus increasing susceptibility to infections[15,16]. However, iron supplementation has also been implicated in cellular damage mediated through free radicals[17]. In an attempt to better understand the effects of iron supplementation on the incidence of infectious illnesses in children, a review was conducted by Gera and Sachdev[18]. 28 randomised controlled trials comparing the effect of iron supplementation versus placebo on 7,982 children with the incidence of infectious disease as the outcome were included. The pooled estimate of the incidence rate ratio (iron versus placebo) for all recorded infections was 1.02 (95% CI 0.96 to 1.08, *P*=0.54). The incidence rate difference (iron minus placebo) for all recorded infections was 0.06 episodes per child per year (95% CI -0.06 to 0.18, *P*=0.34). However, there was a slight increase in the risk of developing diarrhoea (incidence rate ratio 1.11 comparing iron versus placebo, 95% CI 1.01 to 1.32, *P*=0.04). The overall conclusion from the review was that iron supplementation had no apparent harmful effect on the overall incidence of infectious illnesses in children. The higher risk of diarrhoea could not be directly attributed to increased gastrointestinal infections as it could be the consequence of an irritant effect of iron on gut motility.

Thrombosis

IDA has been reported to be associated with cerebral vein thrombosis[19]. In a large case-control study from a comprehensive Stroke Registry in Canada, previously healthy children were 10 times more likely to have IDA than healthy children without stroke, suggesting that IDA is a significant risk factor for stroke in otherwise healthy young children[20]. Three mechanisms have been postulated: a hypercoagulable state directly related to ID and/or anaemia; thrombocytosis secondary to IDA; and anaemic hypoxia, whereby a mismatch between oxygen supply and end-artery oxygen demand leads to ischaemia and infarction[21].

IRON METABOLISM-A BRIEF OVERVIEW

The typical body iron content of an adult male is 4g, of which about 2.5g circulates as Hb, 1g is stored predominantly in hepatocytes and reticuloendothelial macrophages, and the rest is distributed in myoglobin, cytochromes, and other ferroproteins. Full-term infants are born with 180mg of iron, but must double their red cell mass within 12 months.

Only about 1–2mg is lost from the body daily, predominantly through desquamation and minor blood loss, so body iron stores are regulated mainly through iron absorption. Haem iron from animal sources is better absorbed than non-haem iron, thus ID is less frequently seen where meat constitutes a significant part of the diet. The specific mechanism of haem iron absorption remains unclear. Non-haem iron is best absorbed in the ferrous form (Fe^{2+}). Reduction of ferric iron (Fe^{3+}) by gastric acid or dietary ascorbic acid (Vitamin C) optimises absorption. Transport of non-haem iron across the luminal surface of duodenal enterocytes occurs via a specific divalent metal transporter protein, known as DMT1[22]. It is released into the circulation via ferroportin where it binds to transferrin.

Transferrin is the carrier of iron in plasma. Transferrin receptors on the surface of erythrocyte precursors accept iron-transferrin complexes. These undergo endocytosis and the iron is incorporated into Hb while transferrin receptor-transferrin complex is recycled to the cell surface, where transferrin is released back into circulation. Hepatocytes and macrophages take up iron both via transferrin receptors and alternative pathways, and store iron as soluble ferritin.

Senescent red cells are phagocytosed by macrophages, where iron is released from haem and can be either utilised directly by the cell, exported via ferroportin or stored as ferritin, completing the iron metabolism cycle.

A recent development in the understanding of iron metabolism came about with the discovery of hepcidin in the early 2000s[23]. Hepcidin is a peptide hormone synthesised by the liver and plays a central role in systemic iron homeostasis. It controls the release of iron from macrophages by its action on ferroportin, the iron exporter on cell surfaces. Upon binding with hepcidin, ferroportin molecules dissociate from the cell surface membrane and become internalised and degraded[24,25]. This leads to a diminished release of iron from macrophage stores, as well as a diminished export of iron from duodenal enterocytes, resulting in decreased serum iron[24]. Hepcidin synthesis is controlled predominantly at the transcriptional level and is up-regulated by raised plasma iron-transferrin levels, the haemochromatosis protein, transcription factor SMAD4, and bone morphogenetic protein[26,27]. Hepcidin is down-regulated in

response to hyperactive erythropoiesis, IDA, hypoxia, erythropoietin and is potently stimulated by inflammation[28], where it is intimately involved in the pathogenesis of anaemia of chronic disease.

Iron homeostasis at the cellular level is mediated through the interaction of iron-regulatory proteins (IRP1 and IRP2) with iron-regulatory elements (IREs) in messenger ribonucleic acids that encode key iron transporters, ferroproteins, and enzymes involved in iron-utilising pathways. Cellular iron homeostasis ensures that sufficient but not excessive amounts of iron are taken up by each cell to meet its individual requirement for ferroprotein synthesis. The IRE/IRP system effectively regulates iron uptake, provides for the storage of excess iron in ferritin, and coordinates the synthesis of haem, iron–sulphur clusters, and ferroproteins with the availability of iron. The system acts to decrease wasted expenditure of synthetic energy and substrates, and to prevent accumulation of toxic forms of iron.

DIAGNOSIS AND LABORATORY EVALUATION

IDA should be distinguished from other causes of anaemia because of its association with underlying conditions, and because treatment is simple, safe and effective. Conditions that can produce a hypochromic, microcytic anaemia and be confused with IDA include hereditary anaemias (commonly thalassaemia in Singapore) and anaemia of chronic disease (ACD). The initial work-up should always include a thalassaemia screen to exclude concomitant thalassaemia traits. However, it should be noted that co-existing ID can artifactually result in a low HbA_2 level, masking the diagnosis of beta-thalassaemia trait. A repeat thalassaemia screen should be performed if microcytosis persists despite correction of ID.

Various laboratory measurements of iron status are available and are discussed in the following few paragraphs. Table 1 provides a guide for the interpretation of laboratory tests of iron status and the differentiation between ID, IDA, ACD and anaemia of chronic disease with co-existing iron deficiency anaemia (ACD/IDA).

Serum iron

Serum iron exhibits marked diurnal variation with higher concentrations late in the day, and fluctuate according to daily intake. It may transiently reach reference values after the ingestion of meat or oral iron supplements even if true ID is present. Serum iron is also low in the presence of infection and inflammation. The specificity may be increased if fasting iron levels are taken. It should not be used on its own to diagnose ID.

Serum Transferrin / Total iron binding capacity

Serum transferrin is assayed either directly or indirectly as the total iron binding capacity (TIBC) of the patient. It is not affected by inflammation. The transferrin saturation which is derived from

Table 1. Laboratory evaluation of ID, IDA, ACD and ACD/IDA.

Parameters	ID	IDA	ACD	ACD/IDA
Hb	N	↓	↓	↓
MCV	N	↓	N or ↓	N or ↓
Serum iron	↓	↓	↓	↓
Transferrin or TIBC	N or ↓	↑	N	N or ↑
Transferrin saturation (Serum iron/ TIBC)	N or <15%	<15%	N or ↓, usually >15%	N or <15%
Ferritin	<30ug/L	<10–15ug/L	N or ↑	N or ↓, usually <100ug/L
s-TtfR	↑	↑↑	N or ↓	↑
s-TtfR-F index	>2	>2	<1	>2
CHr	↓	↓↓	N	↓
Marrow iron	↓	↓	↑	↓

N= normal; ↓= reduced; ↑= increased; Hb= haemoglobin; MCV= mean corpuscular volume; TIBC= total iron binding capacity; sTfR= soluble transferrin receptor; sTfR-F index= soluble transferrin receptor/log Ferritin index; CHr= reticulocyte haemoglobin concentration

serum iron divided by the TIBC has some value in diagnosing IDA when it is low, but is subject to the same variables as the determination of serum iron. In general, ID is more likely to be present when the transferrin saturation is <15%. Oral contraceptives are known to induce increases in serum transferrin and produce artifactually low transferrin saturation values[29].

Serum Ferritin

Serum ferritin (SF) is a sensitive parameter for the assessment of iron stores in healthy subjects[30-33]; 1g/L of SF corresponds to 8–10mg of available storage iron[33]. Dallman and colleagues suggest a cutoff value of 10g/L for children[31]. However, SF is an acute-phase reactant, thus concentrations of SF may be elevated in the presence of chronic inflammation, infection, malignancy or liver disease. This may make diagnosis of ID in the presence of inflammation a challenge. Markers such as C-reactive protein may be useful to help identify co-existing inflammation.

Soluble Transferrin Receptor

The soluble transferrin receptor assay (sTfR) is a useful measure of iron status and is not affected by inflammation or infection. In plasma, sTfR is a truncated form of the tissue receptor, and its serum concentration is directly proportional to the iron requirement in the cells[34]. When the iron supply is inadequate, there is an upregulation of TfR to enable the cell to compete more effectively for iron, and subsequently, more sTfR is found in serum. An increase in sTfR concentrations is seen in patients with ID or IDA. The test is available in some specialised laboratories in Singapore. However, standard values for infants and children have yet to be established. The ratio of sTfR/log ferritin has been found to be useful in differentiating between IDA, ACD and identifying co-existing ID in patients with ACD[34]. The sTfR/log ferritin ratio is >2 in patients with IDA or ACD/IDA and <1 in patients with ACD alone.

Other Tests of Iron Status

Other tests of iron status available include the reticulocyte Hb concentration (CHr) which is available from several automated haematology analysers in Singapore and can be specially requested for. It is not affected by inflammation, infection or malignancy. The CHr assay provides a measure of iron available to cells recently released from the bone marrow. A low CHr concentration has been shown to be a strong predictor of ID in children[35,36].

Serum hepcidin levels may emerge as a useful tool for assessment of iron status, however it is currently not available as a test in Singapore.

Assessment of marrow iron stores is considered the gold standard for the diagnosis of ID. However, the invasiveness of the test precludes its routine use. In subjects with IDA, marrow iron stores are depleted in both erythroid progenitors as well as macrophages. However, in ACD, iron stains show increased iron in macrophages, but iron is decreased/absent in erythroid precursors.

MANAGEMENT OF IDA

Successful treatment of IDA in infants and young children lies in appropriate dosing and scheduling of oral iron therapy, dietary modifications and follow-up assessment for response.

Oral Therapies

Recommended doses for treatment of IDA are 3–6mg/kg/day of elemental iron, depending on the severity of IDA. For maximal absorption, the supplement should be given between meals and

Table 2. Iron Supplements and Their Elemental Iron Content.

Iron supplement	Elemental iron content
Iron polymaltose drops	50mg/mL
Iron polymaltose syrup	50mg/5mL
Ferrous fumarate	65mg/200mg tablet
Ferrous gluconate (Sangobion)	30mg/250mg capsule
Iron sulphate (Nutroplex liquid with iron and lysine)	15mg/5mL

Recommended doses for treatment of IDA are 3–6mg/kg/day of elemental iron

with juice. Iron absorption is increased if the iron supplement is given with juice rather than milk[37]. Table 2 summarises the elemental iron content of common iron supplements available locally.

Dietary Modifications

Appropriate dietary changes with the introduction of iron-containing complementary foods after four to six months of age is advised. Red meats, cereals fortified with iron, vegetables that contain high levels of iron and fruits with vitamin C should be introduced.

Parenteral Iron Therapy

Parenteral iron therapy should be reserved for patients with severe, persistent anaemia who have proven intolerance to oral supplements, malabsorption, or poor compliance to oral therapy. Intravenous iron sucrose (100mg of elemental iron/5ml) is available locally. However, parenteral iron should be used with caution because of the risk of anaphylaxis[38].

Red Cell Transfusions

Red cell transfusions should only be reserved for patients with severe, symptomatic anaemia compromising end-organ function and should be administered with caution to avoid precipitating cardiac failure.

Assessment of Response

Response to iron replacement therapy can be monitored with serial reticulocyte counts and Hb assessments. After therapeutic doses of oral iron, a reticulocytosis should be seen within 72 hours. The Hb should rise by at least 1g/dL within four weeks. After demonstration of an adequate initial response, the Hb should subsequently be monitored every two to three months until it reaches the age-adjusted normal range. Iron supplements should then be continued for a minimum of three more months to replace storage iron pools. Early discontinuation of iron therapy will frequently lead to recurrence of ID.

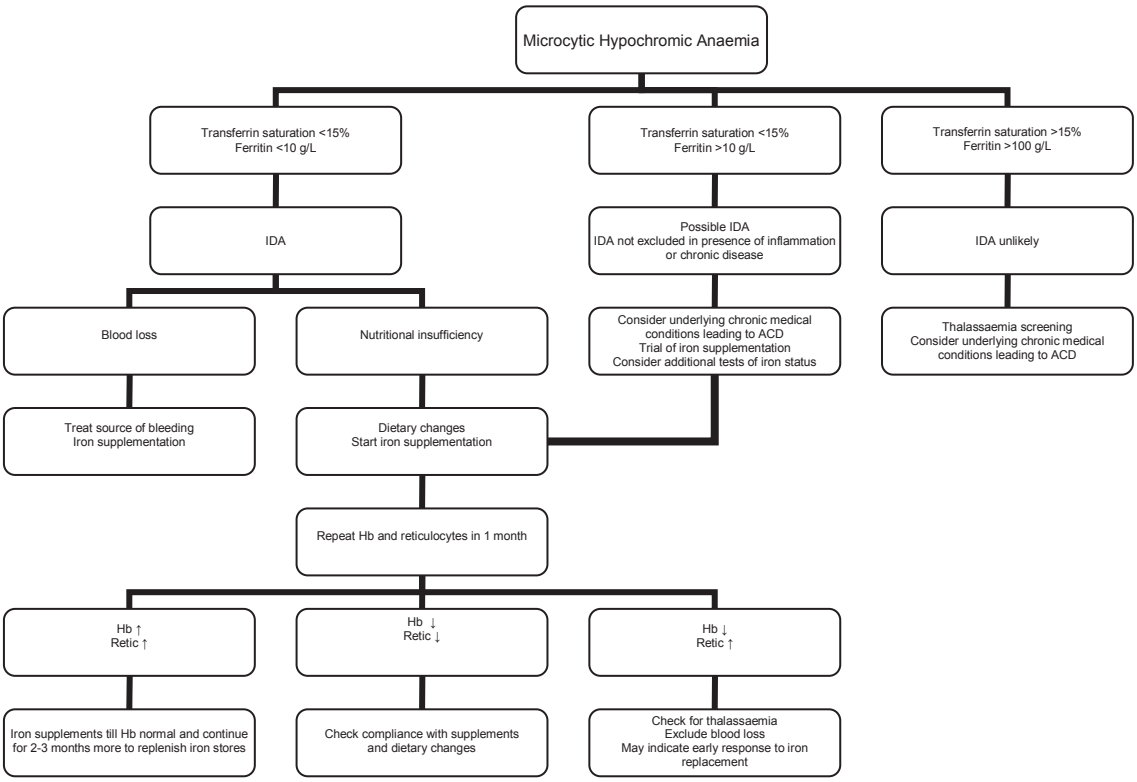

Fig. 1. Approach to diagnosis, management and assessment of treatment response in IDA

Legend:
Transferrin saturation – serum iron/total iron building capacity
IDA – iron deficiency anaemia
ACD – anaemia of chronic disease
Hb – haemoglobin
Retic – reticulocytes

The most common causes for non-responders to iron supplements are compliance failures and intolerance to medication as iron formulations do result in gastric irritation. Parents should be interviewed on whether the supplements have been given at the appropriate dose and timing, whether the appropriate diet modifications have been made, and if there has been a significant intercurrent illness to cause a transient drop in Hb. Ongoing gastrointestinal blood loss or other causes of anaemia also have to be evaluated in non-responders.

Figure 1 summarises the approach towards diagnosis, management and assessment of treatment response in IDA.

PREVENTION OF IDA

Prevention of IDA in children includes ensuring that the daily intake of iron meets the nutritional requirements of the infant or child. The dietary recommendations for iron intake by the American Academy of Pediatrics are as follows[39]:

•In term infants, breastfeeding for the first four to six months.

•Exclusively breastfed term infants should receive iron supplementation of 1mg/kg per day, starting at four months of age and continued until appropriate iron-containing complementary foods have been introduced.

•For partially breastfed infants, the proportion of human milk versus formula is uncertain; therefore, beginning at four months of age, infants who receive more than half of their daily feedings as human milk and who are not receiving iron-containing complementary foods should also receive 1mg/kg per day of supplemental iron.

•For formula-fed infants, iron needs for the first 12 months of life can be met by a standard infant formula (iron content: 10–12mg/L) and the introduction of iron-containing complementary foods after four to six months of age, including iron-fortified cereals.

•Infants less than 12 months of age should not be exclusively fed with cow's milk as the iron content of cow's milk is very low.

•In breastfed preterm or low birth weight infants, elemental iron supplementation (2mg/kg per day; maximum 15mg) is recommended starting at one month of age and is to be continued until 12 months of age.

•Toddlers one through three years of age should have an iron intake of 7mg/day. This would be best delivered by eating red meats, cereals fortified with iron, vegetables that contain high levels of iron and fruits with vitamin C, which augments the absorption of iron.

•For infants and toddlers not receiving their required iron intake, liquid supplements are suitable for children 12 through 36 months of age, and chewable multivitamins can be used for children three years and older.

CONCLUSION

IDA continues to be a common and important childhood health issue with its haematological consequences of anaemia. Paediatricians and other healthcare providers should thus work towards the prevention and elimination of IDA. However, more studies are required to evaluate the neurocognitive and immunity effects of IDA. Early recognition and diagnosis of IDA with appropriate interpretation of laboratory investigations is key to the successful treatment of children with IDA.

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