THE DIAGNOSIS AND PROPHYLAXIS OF THE IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN BABIES AND SMALL CHILDREN

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Abstract

The work refers to the diagnosis and prophylaxis of the iron deficiency and iron deficiency anemia in babies (naturally or artificially fed) and the children younger than 3 years. The recent studies show that iron deficiency anemia and iron deficiency without iron deficiency can have long term effects on neurological development. We hereby present the adequate iron addition and the screening of iron deficiency anemia.

Key words: iron deficiency, iron deficiency anemia, baby, small child, iron addition

Introduction

The iron deficiency and iron deficiency anemia continue to be a world health issue in the developing nations and even in the industrialized ones (2,23,28). Nevertheless, even more important than anemia is the iron deficiency without anemia which can have long term effects on the neurological development and behavior, some of them irreversible. This work refers to the diagnosis and prophylaxis of iron deficiency anemia.

Definition, prevalence and necessary iron

Anemia is defined as the drop in concentration of the hemoglobin under 11g/dL in children aged between 12 and 36 months. In certain populations (such as the ones leaving at high altitudes) the value adjustment must be done.

The normal iron concentration is the situation in which there is enough iron to maintain the physiological functions within normal limits. The iron deficiency is the situation in which there is not enough iron to maintain the physiological functions within normal limits. The iron deficiency is the result of the inadequate absorption of iron reported to the needs or of the negative balance of iron on long term. Each of these situations leads to the decrease in the iron deposits measured in serum ferritin or in the iron concentration in the bone marrow. The iron deficiency may or may not be accompanied by iron deficiency anemia. The iron deficiency anemia is the anemia resulting from the iron deficiency (2,16,18).

The iron overload is the excessive accumulation of iron in the tissues. The iron overload is usually the result of the genetic predisposition to excessively absorb and store iron (e.g. hereditary hemochromatosis). The iron overload may also be a complication in other hematologic diseases that need repeated blood transfusions, repeated iron injections or excessive iron ingestion.

The recommended iron diet is the average of the daily iron needs that is enough for almost all individuals, based on age and gender. The adequate iron need is the term used when there is not enough information to establish the recommended diet for certain population segments (newborns, babies younger than 6 months)

80% if the iron quantity of the new born at birth is formed during the last pregnancy trimester. The premature newborn “skips” this period and has an iron deficiency. Certain diseases of the mother, such as anemia, sugar diabetes, arterial hypertension with in-uterus growth deficiency, can lead to low iron deposits in the newborns born on time, as well as the premature ones. The iron deficiency in premature babies increases with the decrease of the gestational age and is worsened by the frequent phlebotomies without adequate blood replacement. On the other hand the premature babies who receive multiple blood transfusions run the risk of iron overload. The varying status in blood in premature babies, with the risk of iron deficiency or toxicity, makes the determination of the exact needs impossible, which is estimated at 2-4 mg/day if administered orally (1,12,28).

IOM (Institute of Medicine), taking into account the average iron content of the human milk, has determined the adequate intake at 0.27 mg/day in full term newborns since birth until 6 months of age (16).

The average of the iron content of the human milk if 0.37 mg/L and the average of the milk needs of the exclusively fed baby is estimated at 0.78 L/day. From these valued the necessary amount has been determined at 0.27 mg/day for the full term newborn until 6 months of age. IOM has considered that there must be a direct connection between the age of the baby and the milk ingestion; thus there must not be any correlation based on weight. Nevertheless, there is a large variation in the iron concentration in human milk and there is no guarantee that it will cover the needs of the baby. For the babies between 6 and 12 months the recommended diet for iron (according to IOM) is of 11 mg/day (16).

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The amount of iron losses – the epithelial exfoliation of the skin, the urinary and digestive tracts – was added to the amount of the iron needs for the increase of the blood volume with the growth of tissue mass and to the iron deposits of that period. It is mentioned that the necessary iron in babies does not pass directly from 0.27 mg/day to 11 mg/day at the age of 6 months. It is obvious that the full term healthy newborn needs very little iron in the first 6 months as compared to the needs after 6 months (16,25).

Using the same reasoning, IOM considers that that recommended necessary iron for the child aged 1-3 is of 7 mg/day.

There is no national statistic on the prevalence of iron deficiency and iron deficiency anemia in babies. The general prevalence in the USA of iron deficiency anemia has dropped in babies and small children since the 1970s, with the use of iron-enriched milk formulae and with the drop of the use of cow milk in babies (2). Related the iron deficiency anemia is the issue of the interaction between iron and led. If the studies made on animals and humans it has been noticed that the iron deficiency anemia increases the intestinal absorption of led. Thus, iron deficiency anemia decreases the efficiency of lead chelators and the iron supplements correct this issue (7,38).

Many studies have shown the connection between iron deficiency anemia and later cognitive deficiencies. Lozoff et colab. (2006) have shown the cognitive deficiencies in the 1-2 decades after iron deficiency during the baby stage (18). Nevertheless, it is difficult to determine a causality connection. It is known that iron is essential in neurological development. The iron deficiency affects the neuronal metabolism, the neurotransmitter metabolism, the mielinisition and memory (6,11,30). These observations could explain the behavioral problems in children with iron deficiency.

Paraclinical diagnosis

We follow certain parameters: the hemoglobin concentration, the reticulocites, erythrocitary indexes, the total iron assimilation, the transferrine saturation, protoporphyrine, ferritine and sTfr (transferrine receptor). The last parameter, the soluble form of the transferrine receptor that freely travels into the plasma, is an important indicator of the status of iron in the organism.

In this **table** we show the changed in the main parameters.

Parameter	Iron deficiency without anemia	Iron deficiency anemia	Iron overload
Ferritine	↓	↓↓	↑
Transferrine saturation	↓	↓	↑↑
Transferrine receptor (sTfr)	↑↑	↑↑↑	↓
Reticulocitary hemoglobin	↓	↓	Normal
Hemoglobin	normal	↓	Normal
VEM	normal	↓	normal

↓ low value, ↑ high value

The iron status in children is not determined by a simple determination of hemoglobin concentration. The decrease in hemoglobin can have a variety of causes, of which we mention the hemolitical anemia, the chronic disease anemia, the B12 or folic acid deficiency anemia, the genetic disease anemia. But once put the iron deficiency diagnosis, the supervision of the hemoglobin concentration is a good response measure to the treatment.

Any set of analysis will include the hemoglobin concentration to determine whether or not there is anemia. The three parameters giving selective data about the status of the iron are: ferritine, reticulocitary hemoglobin and the transferrine receptor.

Ferritine is a sensitive parameter for the assessment of the iron deposits in healthy subjects (1 µg/L of ferritine corresponds to 8-10 mg of available iron). In children the value showing the depletion of the iron deposits is of 10 µg/L (in adults 12 µg/L) (9,17). Because the serum ferritine is a short phase reactant, its concentration can be increased in the presence of chronic inflammations, infections, malignancies, hepatic diseases. A simultaneous determination of protein C reactive is needed to exclude the inflammation.

Even though serum ferritine has a lower accuracy that reticulocitary hemoglobin or the transferrine recepton, the combination of ferritine and protein C reactive is more accessible and a more reliable test as long as the protein C reactive is not high (9,17,34).

The reticulocitary hemoglobin and the transferrine receptor are not influenced by the inflammation, malignancy, infections, chronic diseases and are preferable for the diagnosis. The reticulocitary hemoglobin has been validated, standardized in children and actually available. This parameter provides a measurement of the available iron in the cells recently released by the bone marrow (5). The reticulocitary hemoglobin can be measured by citometric flow and the low concentration is the most important in predicting iron deficiency in children.

The transferrine receptor (sTfr) is a measure of the iron status which finds the iron deficiency on a cellular level (32,37). It is found on the cell membrane and allows the transfer of iron in the cell. When the iron is insufficient, there is an imbalance of the transferrine receptor's permission for the cell to have a more efficient iron composition and later its circular form has a serum increase. An increase in serum in the transferine receptor can be found in the patients with iron deficiency or iron deficiency anemia, even though the serum doesn't increase until the iron deposits are depleted in the adults. The assessment of the transferrine receptor is not usually available and the standard value for children has not yet been established.

For putting the diagnosis of iron deficiency anemia (when a hemoglobin value smaller than 11g/dl is associated), nowadays the following tests can be used: ferritine + protein C reactive or reticulocitary hemoglobin. For the iron deficiency diagnosis without anemia the same parameters are measured.

Another approach in the diagnosis of iron deficiency anemia in mild anemia children (Hb 10-11g/dL) is the monitoring of the response to iron supplements, especially if the history of the nutrition involves an iron-poor diet. An increase in hemoglobin of 1 g/dL after 1 months of treatment is used as positive for iron deficiency anemia. This approach imposes an adequate iron treatment, the compliance of the patient and an adequate absorption.

Correcting the iron deficiency and iron deficiency anemia.

Premature babies. The naturally-fed premature babies (below 37 weeks of gestational age) will receive elementary iron supplements of 2 mg/kg/day beginning with 1 month of age until 12 months. The iron can be provided through medication or through an iron-rich diet. The premature babies who are fed with formulae for premature babies (14.6 mg iron/L) or ordinary formulae (12 mg iron/L) will receive approximately 1.8-2.2 mg/kg/day assuming a milk consumption of 150 ml/kg/day (12,29).

Despite the iron-enriched formulae, 14% of premature babies have an iron deficiency between 4 and 8 months of age. Thus the enriched formulae need an iron supplement addition. The exception for these iron supplements are the premature babies who received multiple transfusions during the hospitalization period, who might not need iron supplements.

Naturally fed full term babies. The full term baby has a higher hemoglobin concentration and a higher blood volume as compared to body weight. They go through a physiological decrease in hemoglobin and blood volume during the first four months of life. Usually the iron deposits are enough for the first 4-6 months. The iron content of human milk is enough for the newborns who are exclusively naturally fed.

The exclusively natural diet is recommended for 6 months. The exclusively natural diet for the newborns after 6 months is connected to a higher risk of iron deficiency anemia at the age of 9 months. The recommendation for an exclusively natural diet does not take into account the babies born with low iron deposits (the newborns with a low weight at birth, the babies whose mothers have diabetes), a situation which also determines a low iron concentration at the age of 9 months.

It is recommended that the full term babies who are exclusively naturally fed receive an iron supplement of 1 mg/kg/day starting with the age of 4 months until the introduction of the iron-rich foods (10,25).

For the mixed-fed babies, the proportion of the breast-feeding as opposed to the formulae is uncertain. Thus, after 4 months the babies who do not receive an iron-rich diet will get 1 mg/kgc/day supplemental iron.

Artificially fed full term babies. The American Pediatric Association has concluded that the milk formulae containing 12 mg elemental iron /L are safe (26,27,31). There is not enough data to relate the formulae with 12 mg/L to the gastro-intestinal symptoms (3,12,31).

Small children (1-3 years). The necessary iron in small children is of 7 mg/day. Ideally, the necessary iron must be provided through food naturally rich in iron and vitamin C which stimulates the iron absorption. In the developing countries, the necessary iron is covered by the iron strengthening of certain foods such as corn flour, soy sauce, rice, cereal. Nevertheless, there are barriers to providing an optimal iron intake: the lack of education of the parents, the low compliance to any digestive adverse effects, the price of enriched products, the federal nutrition programs which do not provide iron supplements. In the US, the iron-enriching of formulae and cereals for the babies has lead to the decrease of iron deficiency anemia (2).

As an alternative for those who do not take enough iron from the diet, there are also the iron supplements which are available as a component of the multivitamin syrup or chewable tablets (4,13,14).

Screening for iron deficiency and iron deficiency anemia.

The universal screening must assess the risk factors associated to the iron deficiency/iron deficiency anemia: a history of premature birth or small weight at birth, exposure to led, an exclusively natural diet over 4 months without iron supplements, an integral milk diet, a diet of non-iron enriched cereal or of low-iron foods. The additional risk factors include nutrition problems, an inadequate diet, a stationary weight curve.

In the US 60% of the anemia cases are not due to the iron deficiency and most of the iron deficiency children do not have anemia.

Selective screening tests can be done at any age when the risk factors for iron deficiency and iron deficiency anemia are found.

After determining the hemoglobin concentration, in children with hemoglobin below 11 mg/dL or with a high risk of iron deficiency the ferritine + protein C reactive and reticulocitary hemoglobin are determined. The determination of the transferrine receptor will enter the screening tests once the value in children is determined.

Conclusions

It is important that we eliminate the iron deficiency and iron deficiency anemia in babies and young children, considering their impact on cognitive and behavioral development(22,24,30). There are controversies regarding the time and methods of screening and on the use of iron supplements.

The present data support the following recommendations:

• Healthy newborns born on time have enough iron for at least the first four months of life. The exclusively natural feeding after the first four months without iron supplements leads to an iron deficiency. The naturally fed babies must receive 1 mg/kg/day starting with the age of 4 months until the iron-rich foods (including cereal) are introduced in the diet.
• For the mixed-fed babies, the proportion of mother milk vs. formula is uncertain. Consequently, starting with the age of 4 months the mixed-fed babies who do not receive iron-rich foods must receive 1 mg elemental iron/kg/day.
• For the formulae-fed babies, the necessary iron can be covered by standard milk formulae (iron content 10-12 mg/L) and the introduction of foods containing iron after 4-6 months of age, including cereal. The integral milk must not be used before 1 year of age.
• The iron addition between 6 and 12 months must be of 11 mg/day. When the food becomes more varied, the vegetables and red meat with a high iron content are introduced. If the food does not cover the necessary, the liquid iron supplements will be introduced.
• The small child (1-3 years) has a necessary of iron of 7 mg/day which will be provided by the red meat, iron-enriched cereal, iron-rich vegetables, fruit with vitamin C which increases the iron absorption (35,36). In the case of the children who do not receive the appropriate iron-rich food, iron supplements are recommended as syrup or chewing tablets.
• Premature babies must receive an iron addition of at least 2 mg/kg/day until 12 months old, including the supplementary iron in the milk formulae. Naturally fed premature babies must receive iron supplements of 2 mg/kg/day after 1 months of age until the diversifying with iron-rich foods (29). The exception consists of the premature babies who have received iron through blood transfusions and erythrocitary mass transfusions.
• The universal anemia screening must be done at approximately 12 months with the determination of the hemoglobin concentration and the assessment of the risk factors related to the iron deficiency/ iron deficiency anemia. These risk factors include precarious socio-economic status, a history of premature birth or small weight at birth, exposure to led, exclusively natural nutrition until 4 months of age without iron supplements, iron-rich foods and iron-enriched cereal. Additional risk factors are the eating disorders, inadequate weight gain, inadequate nutrition. In the case of babies and small children, the screening must be done whenever the risk factors are involved.
• If the hemoglobin level is less than 11 mg/dL at 12 months the cause of the anemia will be investigated. If there are risk factors of iron deficiency the status of the iron will be investigated. The ferritin + reactive protein C and reticulocitary hemoglobin will be determined. Afterwards the correct treatment will be applied.
• If a child has mild anemia (Hb 10-11 mg/dL) and can be closely monitored, an alternative diagnosis method will be the increase by 1g/dl of the hemoglobin concentration after a month of iron therapy.
• The use of the transferrin receptor (sTfs) as screening for the iron deficiency is promising and the establishing of the standard value is expected for the use on babies and small children.

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