Academic Journal of
Pediatrics & Neonatology
ISSN 2474-7521

Juniper Publishers
key to the Researchers

Research Article
Volume 2 Issue 4 – January 2017
DOI: 10.19080/AJPN.2017.02.555592

Acad J Ped Neonatol

Iron Deficiency: Beyond Anemia

Bharat J Parmar*, Jwal Doctor, Ruhi, Ashmita and Danu

B J Medical College, Civil Hospital, India

Submission: November 14, 2016; **Published:** January 24, 2017

***Corresponding author:** Bharat J Parmar, B J Medical College, Civil Hospital, Institute of Pharmacy, Nirma University, S.G Highway, Gandhinagar, Ahmedabad 382481 Gujarat India, Email: bjpdr@hotmail.com

Abstract

Iron deficiency is most common nutritional disorder affecting at least one third of world population. Iron is crucial to biologic functions, including respiration, energy production, DNA synthesis, and cell proliferation. Impaired brain development and cognitive, behavioral and psychomotor impairment are worrisome manifestation of iron deficiency. Studies have demonstrated that some of the changes occurring during period of brain growth spurt (<2 years age) may be irreversible. Association of iron deficiency with febrile convulsion, pica, breath holding spells, restless leg syndrome and thrombosis is increasingly being recognized. Impaired cell-mediated immunity and bactericidal function are generally noted in iron deficiency however, the findings are inconsistent.

Keywords: Iron deficiency anemia; impaired Cognition; Breath holding spells; Pica Febrile convulsion; Thrombosis; Infections

Introduction

It is estimated that more than 1.5 billion people affected globally. One third of the world population suffers from Iron deficiency anemia of which 90% live in developing third world. Iron is the most important component of hemoglobin. Iron deficiency is the most common cause of nutritional anemia and commonly occurs during period of increased requirement e.g. in infancy, adolescence pregnancy and during lactation especially among the people with poor socioeconomic status due to inadequate intake of dietary iron, infestation, infections, and malabsorption Anemia is just one manifestation of iron deficiency. Pallor is seen over the face, palm, nail and tongue. The child may like to eat inedible objects such as clay and mud (pica). The child may not be playful and active because of easy fatigability. Anemic children are susceptible to develop frequent infection. Iron deficiency during early life has been seen shown to slow neurodevelopment, cause attention deficit hyperactivity disorders, reduce learning capacity, and predispose to development of febrile convulsion. Iron deficiency result in to conduct disorders, significantly lower scholastics performance, reduces cognitive performance, breath holding spells and papilledema.

Pathophysiology

Iron plays an essential role in the synthesis of hemoglobin. It is unique in that it takes up and releases oxygen with no energy expenditure. Large amounts of the iron are recycled daily from the breakdown from the destroyed red cells. Dietary iron occurs in two forms. Heme iron from animal proteins is better absorbed than non heme iron. Non heme iron is obtained from plant foods and vegetables and is absorbed in the ferrous form mostly in the duodenum and to a lesser extent in the jejunum and proximal ileum. Absorbed iron from the intestinal lumen is transported with a divalent metal protein (DMT) across the mucosal border. From the enterocyte the iron reaches the plasma by the specific transporter proteins called ferroprotein. The primary mechanism of iron homeostasis is regulated by hepcidin.

Hepcidin level decreases in iron deficiency and increases in inflammation and iron excess. The elevated hepcidin blocks the ferroprotein and limits the mobilization of iron in to the plasma. Iron circulates the blood bound to the transferring. Bone marrow erythroblasts have receptors for the iron transferrin complex and the iron complex enters the cells by the endocytosis for the hemoglobin synthesis. The absorption of iron is regulated by iron deficiency (absorption increases), inflammation and iron repletion (absorption decreases), mediated by hepcidin.

Over 90% of the dietary iron for infants and young children are non heme iron. Only 10% of dietary non heme iron is absorbed. The absorption of non heme iron is highly altered by the dietary factors. Food rich in Vitamin C like orange juice, meat and fish enhance iron absorption; calcium, phosphate, tannin in tae and bran decreases the absorption. Breast milk iron, present in

low concentration is well absorbed; cow milk contains high level calcium and phosphorus that interfere with iron absorption [1-5].

Stages of iron deficiency

First stage: A decrease in concentration of serum ferritin.

Second stage: Hb concentration is normal or the normal range, low serum iron concentration and transferring saturation, increase in total iron binding capacity.

Third stage: Decrease Haemoglobin associated with low MCV & MCH and high RDW (Figure 1).

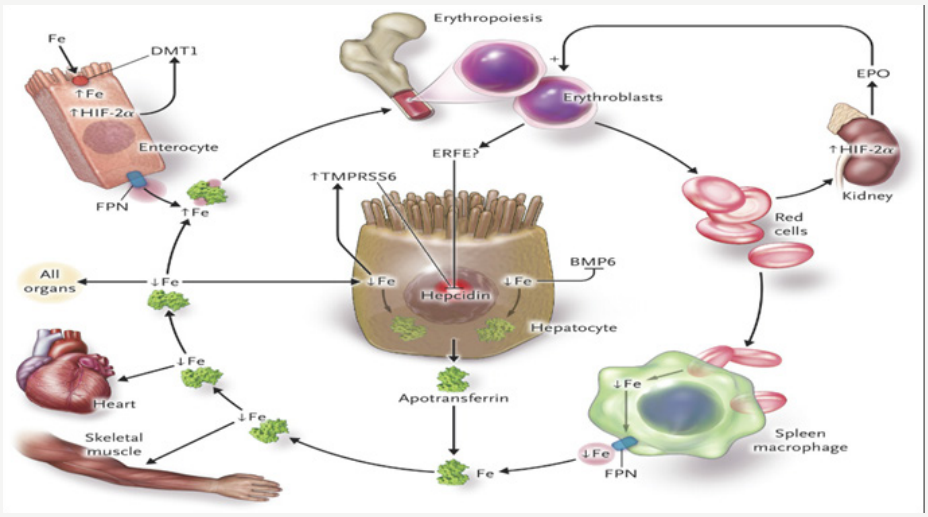

Figure 1: The Iron Cycle -Mechanisms of Adaptation to Iron Deficiency.

Iron and Brain

Behavioral and cognitive dysfunction are must worrisome manifestation of iron deficiency. Recent research has revealed that anemia is late manifestation of iron deficiency, brain deficiency occurs even with normal level of hemoglobin, as iron is most important to red blood cells over all other organs including brain. The biological basis of the behavioral and cognitive development delays due to abnormalities in neurotransmitter metabolism, decreased myelin formation and alterations in brain energy metabolism [6].

IDA and Infants < 2 years age

In Infants adverse effects of iron deficiency on behavior are special concern because the latter part of brain spurt coincides with the period in which iron deficiency anemia is most prevalent (6-24 month). Observational studies have suggested that iron deficient children have lower IQ scores, decreased attentiveness and lower scores on tests of academic performance compare with non anemic controls. These studies indicates that iron deficiency anemia in infancy, perhaps of particular severity and chronicity, has irreversible cognitive impairment [7].

IDA in Children > 2 years Age

Observational studies in children over 2 years have reported poorer cognition and school achievement in iron deficient children. Adolescent girls are prone to develop iron deficiency because of poor dietary intake along with increased iron requirement related to rapid growth and menstrual blood loss and are at greater risk of cognitive impairment [8].

Preventive Trials

Two recent trials reported beneficial effects of iron therapy in infancy. Developmental and behavioral benefits from iron supplementation in infancy.

IDA and Pica

The word Pica is derived from latin root meaning magpie, a bird capable of eating a variety of things. Lanzkowsky define Pica as "a perversion of appetite with persistent and purposeful ingestion of non nutritive substances like Pica includes geophagia (dirt or clay ingestion) tricophagia (hair ingestion), amylophagia (starch ingestion) and pagophagia (ice ingestion). It is a well documented feature of iron deficiency anemia in children.

IDA and Breath Holding Spells (BHS)

The low hemoglobin cause rapid cerebral anoxia due to decreased oxygen carrying capacity of blood that in turn lead to Breath holding spells. Anemic children being irritable may be more predisposed to breath holding spells. Iron therapy should more remarkable therapeutic beneficial in controlling the spells in children with evidence of iron deficiency. Iron has role as a cofactor in catecholamine metabolism in central nervous system. Clinical profile and hematological associations of BHS as result of interaction of cerebral erythropoietin, nitric oxide and interleukin 1 [10-13].

IDA and Febrile Seizure

Febrile seizures are the most common type of seizures, occurring in 2-5% of all children. Kebrinsky et al studied the role of iron in febrile seizures and they reported significantly

How to cite this article: Bharat J P, Jwal D, Ruhi, Ashmita, Danu. Iron Deficiency: Beyond Anemia. Acad J Ped Neonatol. 2017; 2(4): 555592. DOI: 10.19080/AJPN.2017.02.555592

increased incidence of iron deficiency in non seizures compared to seizure group. Iron deficiency may increase frequency of febrile convulsion. Exact etiology of febrile seizures is not known however depend on metabolism of several neurotransmitters, enzyme activities and cerebral erythropoietin has been postulated as causative factor for seizures [14].

IDA and Stroke

Iron deficiency anemia is significant risk factor for stroke in otherwise healthy young children. This increased incidence of thrombotic complications in IDA due to various factors. Increased level of erythropoietin in IDA has been incriminated to have a possible role in stimulating megskaryopoesis, resulting in thrombocytosis. Recently, Bilic & Bilic [5] have reported that amino acid sequences homology of thrombopoietin and erythropoietin may explain the thrombocytosis in children with iron deficiency anemia. In addition to the increased thrombotic risk associated with high platelet count, other possible mechanism suggested is decreased in antioxidant defense in iron deficiency anemia result in to increased oxidative stress, prone to develop platelet aggregation. Reduced deformability and increased viscosity of microcytic red blood cells in iron deficiency may contributory by affecting blood flow patterns within the vessels. Furthermore, anemic hypoxia secondary to iron deficiency could precipitate situations of increased metabolic stress (i.e. infection) at risk area of brain supplied by end arteries, such as the basal ganglia, thalamus and hypothalamus resulting in stroke [15,16].

IDA and Restless Leg Syndrome (RLS)

Restless leg syndrome is characterized by repeated aphasic involuntary muscles contractions. It is mostly reported in adult patient and largely under reported from pediatric population. Although most of the cases with RLS are idiopathic or hereditary; decreased brain iron content and metabolism can lead to RLA. Iron deficiency state may precipitate RLS in as much as 25-30% of people. MRI studies have demonstrated decreased iron content in substantia nigra and red nucleus. Fatigue decrease productivity and decrease learning capacity with iron deficiency [17-20].

Iron and Infection

Iron is required for normal immune function, cell differentiation and growth. Iron is also required for peroxide generating mechanism, cytokine production and myeloperoxidase function in neutrophil. Impaired cell-mediated immunity and bactericidal function are generally noted in iron deficient children; however, the findings are inconsistent. Impaired immunity result into repeated infection [21-25].

Iron and Temperature Regulation

Iron deficiency anemia more readily become hypothermic and have depress thyroid function.

Iron and Growth

Iron deficiency anemia result into impaired growth [26].

Celiac Disease

Malabsorption of iron and result into iron deficiency anemia [27].

Prematurity

Preterm baby due to low iron store and more to growth result into iron deficiency anemia.

Vitamin A and iron deficiency anemia

Deficiency of Vitamin A Limit Mobilization of Iron from Its Stored Site hence Causing Iron Deficiency Anemia [25].

Hook worn infestation

Having hook worn infestation in children decrease level of blood hence increasing iron demand.

Conclusion

Being most common nutritional disorder, it is imperative to recognize effects and long term consequences of iron deficiency. Though anemia is common, iron deficiency state without anemia is largely under-recognized. Studies have reported lower cognitive scores even in children with iron deficiency without anemia. Irreversible cognitive impairment has been reported in children who experienced iron deficiency during period of critical brain growth (<2 years of age). Iron deficiency anemia is highly prevalent in India (reported 55.7% to 85.1% in different states in NFHS-3) and much larger population having iron deficiency without anemia; hence it is critical to recognize the cognitive impairment and treat early [28,29].

Point to be Remember

- Iron Deficiency is most common preventable nutritional deficiency in the world, especially among infants and young children.
- Prevalence of iron deficiency anemia among children under 5 year of age has been estimated to be 75% in India.
- Iron deficiency has adverse effect on physical, mental, emotional, cognitive performance.
- The role of iron deficiency in precipitating febrile convulsion breath holding spell, hyper cyanotic blue spell and infection.
- Iron deficiency has been frequent association of tendency of pica. Pica is common symptoms which predisposes to consumption of lead resulting in plumbism.
- Long term consequences of iron deficiency are poor growth & development, depressed immune function and behavioral changes.
- Serum ferritin along with C-reactive protein serves as best indicator of body iron store.
- The committee of nutrition of the American Academy of Pediatrics recommends the hemoglobin <11 gm/dl and serum

How to cite this article:Bharat J P, Jwal D, Ruhi, Ashmita, Danu. Iron Deficiency: Beyond Anemia. Acad J Ped Neonatol. 2017; 2(4): 555592. DOI: 10.19080/AJPN.2017.02.555592

ferritin <10 mcg/L as diagnostic of iron deficiency anemia in presence of normal CRP.

- The absorption of iron is regulated by iron deficiency (absorption increases), inflammation and iron repletion (absorption decreases), mediated by hepcidin.

Acknowledgement

The authors wish to thank B.J Medical College Civil Hospital Ahmadabad for support this work.

References

1. Berg AT (1992) Febrile seizures and epilepsy: The contribution of epidemiology. Pediatrics Epidermiology 6(2): 192-195.
2. Lozoff B (2000) Perinatal iron deficiency and the developing brain. Pediatr Res 48(2):137-139.
3. Basta SS, Soekirman, Karyadi D, Scrimshaw NS (1979) Iron Deficiency anemia and the productivity of adult males in indonesia. Am Clin Nutr 32(4): 916-925.
4. Bhaskaram C, Reddy V (1975) Cell Mediated immunity in iron and vitamin deficiency Children. Br Med J 3(5982): 522-526.
5. Bilic E, Bilic E (2003) Amino acid sequence homology of thrombopoietin and erythropoietin may explain thrombocytosis in children with iron deficiency anemia. J Pediatr Hematol Oncol 25(8): 675-676.
6. Daoud AS, Batieha A, al-Sheyyab M, Abuekteish F, Hijazi S (1997) Effectiveness of iron theraphy on breath -holding spells. J Pediatr 130(4): 547-550.
7. DiMario FJ, Burleson JA (1993) Autonomic nervous system function in severe breath holding spells. Pediatr Neurol 9(4): 268-274.
8. Berg AT (1992) Febrile seizures and epilepsy: the contributions of epidemiology. Paediatr Perinat Epidemiol 6(2): 145-152.
9. Grantham-McGregor S, Ani C (2001) A review of studies on the effects of iron deficiency on cognitive development in children. J Nutr 131(2S-2): 649-685.
10. Holowach J, Thurston DL (1963) Breath holding spells anemia. N Engl J Med 268: 21-23.
11. Beard J (2003) Iron deficiency alters brain development and functioning. J Nutr 133(5 Suppl 1): 1468S-1472S.
12. Saloojee H, Pettifor JM (2001) Iron deficiency and impaired child development. BMJ 323(7326): 1377-1378.
13. Ghosh K (2006) Non haematological effects of iron deficiency anemia a perspective. Indian J Med Sci 60(1): 30-37.
14. Lanzkowsky P (1959) Investigation into aetiology and treatment of Pica. Arch Dis Child 34(174): 140-148.
15. Lokeshwar MR, Manglani M, Rao S, Patel S, Kullnami M (1990) Iron deficiency anemia-clinical manifestation and management. In: Mehta MN and Kulkarni M (Eds.), Child Nutrition -The Indian Scene. L.T.M. Medical College and Hospital, Bombay, India, pp. 269-295.
16. Masuda S, Okano M, Yamagishi K, Nagao M, Ueda M, et al. (1994) A novel site of erythropoitin production : oxygen dependant production in cultured rat astrocytes. J Biol Chem 269(30): 19488-19493.
17. Mocan H, Yildiran A, Orhan F, Erduran E (1999) Breath holding spells in 91 children and response to treatment with iron. Arch Dis Child 81(3): 261-262.
18. Mocan MC, Mocan H, Aslan Y, Erduran E (1998) Iron theraphy in breath-holding spells and cerebral erythropoeitin. J Pediatr 133(4): 583-584.
19. Panagiotou JP, Douros K (2004) Clincolaboratory findings and treatment of iron-deficiency anemia in childhood. Pediatr Hematol Oncol 21(6): 521-534.
20. Chandra RK (1973) Reduced bacteriocidal capacity of polymorphs in iron deficiency. Arch Dis Child 48(11): 864-866.
21. Oppenheimer SJ (2001) Iron and its relations to immunity and infectious disease. J Nutr 131(2S-2): 616S-633S.
22. Seshadri S (1990) Prevalence and implication of nutritional anemia in children. In: Mehta MN and Kullcarni M (Eds.), Child Nutrition: The Indian Scene. L.T.M. Medical College, Bombay, India, pp. 223-268.
23. Srikantia SG, Prasad JS, Bhaskaram C, Krishnamachari KA (1976) Anemia and immune responce. Lancet 1(7973): 1307-1309.
24. Tekin D, Yavuzer S, Tekin M, Akar N, Cin S (2001) Possible effects of antioxidant status on increased platelet aggregation in childhood iron deficiency anemia. Pediatr Int 43(1): 74-77.
25. Trenkwalder C, Högl B, Winkelmann J (2009) Recent advances in diagnosis, genetics and treatment of Restless leg Syndrome. J Neurol 256(4): 539-553.
26. Viteri FE, Torun B (1974) Anemia and physical work capacity. Clin Hemat 3: 609-626.
27. Xiaoxi Z, Wu T (2007) Iron supplementation for iron deficiency anemia in children (Protocol). The Cochrane Database of Systemic Reviews (2): CD006465.
28. Lukowski AF, Koss M, Burden MJ, Jonides J, Nelson CA, et al. (2010) Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long term deficit in executive function and recognition memory. Nutr Neurosci 13(2): 54-70.
29. Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, et al. (2013) Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol 161(5): 639-648.

DOI: 10.19080/AJPN.2017.02.555592

How to cite this article: Bharat J P, Jwal D, Ruhi, Ashmita, Danu. Iron Deficiency: Beyond Anemia. Acad J Ped Neonatol. 2017; 2(4): 555592. DOI: 10.19080/AJPN.2017.02.555592