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Iron Deficiency and Childhood Morbidity

by

A.H. MARKUM, C. WINDRAJATI MARWOTO, MARIA ABDULSALAM, D. GATOT, I. WAHIDIYAT and S. MUSLICHAN

(From the Department of Child Health, Medical School, University of Indonesia)

Abstract

Although it is likely that individual iron status will influence infections, results of various studies on immune response in iron deficient children remain controversial. This situation is becoming more complicated if projected in clinical field trials where multi and interrelated factors contribute to the occurrence of infection as commonly found in developing countries.

Our results in this field study in semi urban areas which covered 95 children of low and moderate socio-economic families showed that :

1. *Iron deficient children are more susceptible to infection than normal children.*
2. *The frequency of infection is correlated with the severity of iron deficiency, but not with the hemoglobin level.*
3. *In under-nourished children, however, the frequency of infection depends mainly on the nutritional status rather than on the degree of iron deficiency.*

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Introduction

It is generally accepted that iron deficiency is a worldwide problem, and its prevalence as well as its serious complications are mostly found in developing countries. Various studies indicate that iron deficiency is by far the most common cause of nutritional anemia. Therefore it is not surprising that in developing countries iron deficiency may belong to the 4 major problems of nutritional disorders.

Studies in many areas of developing countries have shown that the prevalence of iron deficiency anemia is not less than 50% among under-five children (Lovric, 1976; Thanangkul, 1976; WHO, 1975) and this figure appears higher as the degree of malnutrition increases (Samsudin et al., 1976). Furthermore it is also reported that this disorder is mainly observed in infants and young children of low socio-economic status (Kulapongs, 1975; Soemantri, 1978; Untario et al., 1976).

A still greater incidence of iron deficiency would presumably be detected if iron stores were evaluated (Kimber, 1976). The high incidence of hypoferremia is also common in industrialized countries. The figures from the United States revealed the incidence of 47% in children 1 - 2 years of age, 62% in children of low socio-economic groups, and even still high incidence of 39% is observed in children of upper-middle-class families (Owen et al., 1970).

The concept that iron deficient children are more prone to infections has been recognized by several investigators during the last 2 decades. Although this relationship is still controversial (Buckley, 1975; Burman, 1972; Douglas Wilson, 1974) there are some evidences that infants and children, who have moderate to severe iron deficiency, tend to have more infections than those who are normal (Andelman and Sered, 1966; Douglas-Wilson, 1974; Scrimshaw, 1975; WHO, 1975). Nevertheless, epidemiological studies which attempt to recognize the role of iron deficiency in increasing the rate of infections are difficult to be interpreted, since nutritional status may also interfere the mechanism of this relationship.

Iron in relation to infection susceptibility and host defence

It has long been known that iron deficiency results in a variety of tissue changes and impaired function of many organs (Jacobs, 1969). DNA synthesis, mitosis, enzyme activity are affected adversely by lack of iron. Moreover, iron may have a direct effect on the development of lymphoid tissue and body resistance to infection (Douglas-Wilson, 1974; WHO, 1975). There is an increasing evidence that iron deficiency may play a role in the ability of the individual defence against infection. In the last few years this opinion leads the interest of many investigators to study the mechanism of this functional impairment caused by iron depletion, either through laboratory or epidemiological studies. The body's defence against microorganism depends to a large extent upon 3

major functions : (1) Phagocytic activity of the WBC, (2) Humoral immunity and (3) Cell-mediated immunity.

Some investigators reported that phagocytic activity of WBC was decreased in iron deficient children. Chandra (1973) and Chandra and Saraya (1975) observed a sub-normal activity of the bactericidal capacity of PMN leucocytes and suggested that iron deficiency may also impair the activity of iron dependent enzymes necessary in bacterial killing. A similar result of impaired bactericidal activity has also been obtained by several authors (Arbeter et al., 1971; Higashi et al., 1967; Mac Dougall et al., 1975; Prasad, 1979).

Mac Dougall et al. (1975) further stated that the defect in immune response could be detected in latent iron deficiency before the development of clinical anemia. On the other hand Kulapongs (1975) and Kulapongs et al., (1974) could not confirm the presence of decreased phagocytic activity, since in vitro studies of phagocytosis and killing by PMN cells in their cases of iron deficiency anemia, were entirely normal. In addition, in vitro observations as well as animal studies showed that hypoferremic sera may inhibit the growth of bacteria, which means that the child deficient in iron should respond better than one who is ironreplete. Although there are discrepancies between the results of these various studies, most of the authors believe that significant abnormalities of this particular immune system still exist in iron deficient subjects.

The mechanism of impaired phagocytic function in iron-deficiency is supposed to be related with decreased activity of iron-dependent enzymes. Iron is an integral part of several leucocyte enzyme systems and iron-deficiency may alter their activity. The activity of cytochrome-C and cytochrome oxydase, each of which is an iron-containing enzyme, involved in intracellular oxygen transport and energy production, is reduced in iron-deficient subjects. Several data on cases with iron-deficiency (Higashi et al., 1967; Prasad, 1979; Soemantri, 1978) revealed a significant reduction in MPO activity, the iron-containing enzyme responsible for the bactericidal function of PMN cells.

To some extent iron-deficiency may also alter humoral antibody response. Studies in experimental animals have clearly shown that humoral antibody production was impaired in iron-deficient weanling rats after administration of tetanus toxoid (Nalder et al., 1972). Humoral antibody response in iron-deficient children, however, does not alter significantly compared with a control group of non-iron-deficient. Little differences of the results in various studies are reported, probably due to the influence of infection or antibiotic therapy.

Chandra and Saraya (1975) found a normal antibody response in 16 iron-deficient children, as confirmed by concentration of serum IgG, IgA and IgM, as well as by antibody responses to tetanus toxoid and S. typhi vaccine. Concentrations of C_3 complement were slightly

low, but this reduction was significant only in cases with concurrent infection. In another study (Mac Dougall et al., 1975) it was noted that none of the iron-deficient children had evidence of immunoglobulin deficiency, as judged by the normal serum concentration of IgG, IgA and IgM, and salivary IgA. The anemic children had mean IgG and IgA concentrations significantly higher than the latent iron-deficient subjects, but were not significantly different from the control group. The concentration of C_3 component of complement, however, was significantly higher in children with iron-deficiency, which then returned to normal values after administration of iron compound.

Concerning cell-mediated immune response most investigators are of the same opinion that in iron deficiency a decreased cell- mediated immunity was observed (Srikantia et al., 1976). This finding was proved by the results of various laboratory examinations as shown, for example, by reduced in vitro lymphocyte transformation response to PHA and impaired cutaneous delayed hypersensitivity to several antigens (Chandra and Saraya, 1975; Fletcher et al., 1975; Mac Dougall et al., 1975); reduced DNA synthesis by lymphocytes stimulated with PPD and lower production of macrophage migration inhibition factor in response to PPD and Candida (Joynson et al., 1972). The mechanism of this subnormal immune response is suggested to be the consequence of T-lymphocyte depletion, leading to impairment of DNA synthesis. On the contrary, Kulapongs et al. (1974) could not detect significant defects in cell-mediated immune response of 8 children with severe iron deficiency anemia, since these children had normal PHA-stimulated blastcell transformation and tritiated-thymidine uptake.

A summary of available data on the status of 3 components of host defence in iron deficiency is presented in table 1.

Clinical Implications

As stated above, laboratory investigations indicate the different findings concerning the role of i
ponse. This discrepancy seems to be more complicated if projected into the field of clinical studies. There are clinical situations which support the impression that the availability of iron may contribute to infection, examples of which are as follows :

Breast-fed babies appear to be more resistant to gastroenteritis than to artificially-fed babies and this may be due to lactoferrin in human milk (Bullen et al., 1972). Iron injections when given for the treatment of anemia may make chronic renal infection flare up (Fletcher, 1971); the incidence of malaria increases when iron deficiency anemia is treated (Masawe et al., 1974).

On the contrary, iron deficiency anemia is believed to increase susceptibility to infection; the incidence of gastrointestinal and respiratory tract infections was 40 - 50% greater in infants who did not receive iron supplementation (Andelman and Sered, 1966).

Though there is still a discrepancy, the possible mechanisms make it likely

that individual iron status will influence infections. Nevertheless, the clinical implications of this remain unsettled since more variables may be involved, which must be taken into consideration in order to get reliable clinical results. At least there are 3 major determinants which may influence the clinical findings: (1) Microbial iron metabolism, (2) Host response to infection in iron deficient children, (3) Difficulties in clinical as well as in field trials.

From various studies on microbial iron metabolism, it is generally accepted that transferrin inhibits bacterial growth in vitro by binding iron so tightly that no free iron is available for growth of the micro-organisms. This view is supported by animal studies where growth of bacteria was enhanced by injections of iron, while pretreatment with iron chelating agents confers protection (Lukens, 1975). Since free iron is also necessary for microbial growth, the microorganisms synthesize substances which are capable for binding of iron (siderophores) in order to be able to compete with transferrin. This concept supports the opinion of increased resistance in iron deficient subjects. The second point which may influence the result of clinical findings is the unclarified mechanisms of immune system itself in iron deficient subjects, which have been discussed in detail above. Unreliable data may also be due to many variables involved in making clinical/field trials, as well as to the complexity of materials studied, particularly in developing countries where the difficulties will arise in finding cases of pure iron deficiency, or where infection occurs as the result of multi-related factors.

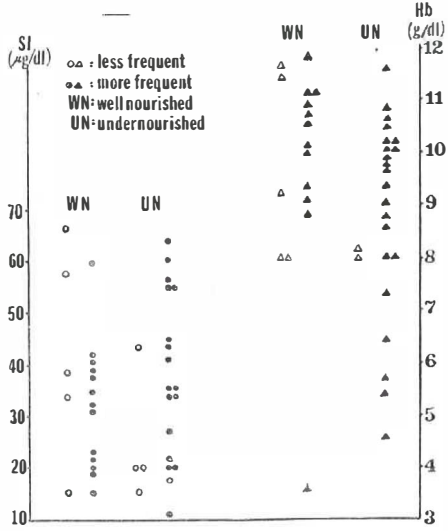
In this context our experiment in semi urban areas will be presented where peripheral blood, serum
capacity, serum ferritin as well
tional status were examined. This investigation which covered 95 iron deficient children of low and moderate socio-economic families revealed that the majority of cases belonged to the second and third degree of iron deficiency (table 2). Only one third of well-nourished children showed the symptoms of anemia in comparison with under-nourished children where two third of cases belonged to the third degree of iron deficiency.

If we consider the relation between the frequency of infection and the stages of iron deficiency, as presented in table 3, it is obvious that iron deficient children are more susceptible to infection than the control group of non-iron deficient, regardless the nutritional status of these children.

Furthermore it is likely that in well-nourished cases a correlation between the frequency of infection and the degree of severity of iron deficiency exists, which is not the case in under-nourished children where the frequency of infection depends mainly on the nutritional status rather than on the severity of iron deficiency.

Figure 1 illustrates also that in well-nourished children the lower the value of serum iron the greater the chance to get infection. On the other hand it seems that there is no correlation between the

FIGURE 1: *Serum iron and hemoglobin levels in relation to frequency of infection*



frequency of infection and the Hb content either in well-nourished or in undernourished groups.

Concerning the relation between infection and the age of cases as illustrated in table 4, it appears that most of the cases being prone to infection are of under-five children, particularly those who belong to the group of under-nourished (80,0%).

Considering the whole problems of the role of iron on body immune response further investigation should be carried out since it is closely related to the country's policy of iron fortification (Bolin, 1976) as well as to the programme of immunization (Nalder et al., 1972), mainly in developing countries where the prevalence of iron deficiency and infection remains very high.

TABLE 1 : *Data on host defense in iron deficiency.*

Authors	Phagocytic function		Humoral immunity		Cell mediated immunity
	Bactericidal killing function	Phagocytosis	Complement	Immuno globulin	
Arbeter et al. 1971	impaired	impaired	—	—	—
Joynson, et al. 1972	—	—	—	—	impaired
Kulapongs, et al. 1974	normal	normal	—	—	normal
Chandra & Saraya, 1973 - 1975	impaired	normal	normal, C_3 (n)	normal	impaired
Fletcher, et al. 1975	—	—	—	—	impaired
Mac Dougall et al. 1975	impaired	—	normal, C_3 ↗	normal	impaired
Prasad, 1979	impaired	—	—	—	—
Srikantia, et al. 1976	—	—	—	—	impaired

TABLE 2 : *Distribution of cases related to stages of iron status.*

	Well-Nourished			Under-Nourished		
Stage	I	II	III	I	II	III
No. of cases	1	36	17	0	14	27
%	68,5%		31,5%	—	34,1%	65,9%

TABLE 3 : *Relationship between stages of iron deficiency and frequency of infection.*

	Well-Nourished		Under-Nourished		Control Group
Stage	II	III	II	III	
No. of cases	27/36	15/17	12/14	24/27	6/38
%	75,0%	88,4%	85,7%	88,8%	15,8%

TABLE 4 : *Frequency of infection in relation to age.*

Age	Well-Nourished		Total	Under-Nourished		Total
	II	III		II	III	
< 5 yrs	9	6	15	7	21	28
> 5 yrs	18	9	27	3	4	7

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