

Iron and infection in the tropics: paediatric clinical correlates

S. J. OPPENHEIMER

Honorary Fellow, Liverpool School of Tropical Medicine, UK

Summary Iron deficiency is prevalent in children worldwide. Programmes of presumptive therapy, mass supplementation and food fortification have been introduced in many countries. The continuing unresolved debate over the interaction of iron and infection in the clinical setting indicates the need for firm guidelines for these practices. Iron overload is associated with increased susceptibility to certain infections, although the exact mechanisms may vary with the main pathology. Iron treatment has been associated with acute exacerbations of infection, in particular malaria. In Papua New Guinea parenteral iron was associated with increased rates of malaria and increased morbidity due to respiratory disease in infants but not in school children. Several subsequent studies in Africa using oral iron showed deleterious effects. In most instances cited, immunity was compromised, and therapeutic doses of oral iron were used. Knowledge of malarial endemicity, immunity with respect to age and the prevalence of haemoglobinopathies is important in planning interventions. A fine balance needs to be struck in the timing and dose of oral iron if informed recommendations are to be made. In parallel with supplementation studies, the effects of iron chelation on infection are being reported increasingly. Such therapy is clearly protective against malaria and some other infections but may predispose to fungal and Yersinia infections.

Introduction

Iron deficiency is the commonest micronutrient deficiency in the world, especially in the tropics, and iron supplementation to children and pregnant mothers is now a worldwide practice.¹

Concern has long existed about the interaction between iron status, iron supplementation and susceptibility to infection. Different authors claim either that iron deficiency helps (the so-called 'nutritional immunity' hypothesis) or hinders defences against infection.^{1,2} While the earlier prospective studies among deprived people in temperate western coun-

tries tended to support the value of iron supplements in reducing rates of respiratory infections in infants, later reports from the tropics seemed to indicate a deleterious effect on susceptibility to both malaria and respiratory infections. The controversy has been compounded by the lack of adequately controlled prospective clinical studies.¹ This review concentrates on the evidence from clinical studies in the tropics, where interactions with malaria are central to the results.

Iron status

Much of the confusion and conflicting results stem from confounding factors which may affect the immune and iron status of the populations under study. These include age, past immune experience, diet and cooking practice, and common inherited disorders of globin

Reprint requests to: Dr S.J. Oppenheimer, 1 Garford Road, Oxford, OX2 6UY, UK. E-mail: stephen.oppenheimer@paediatrics.oxford.ac.uk

Former Wellcome Research Fellow, Tropical Child Health, Liverpool School of Tropical Medicine.

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genes which may, depending on type and zygosity, either protect from malaria or predispose to iron overload. Temporary overload may also result from treatment, in particular using parenteral iron.

Iron deficiency

Few clinical studies convincingly relate states of iron deficiency to susceptibility to infections. This contrasts with the plethora of *in vitro* and *in vivo* animal studies on iron deficiency and infection.

Some studies have noted anaemia in children admitted to hospital for various infections. In these reports, however, causality was not clearly established.³⁻⁵ In an often misquoted study, Masawe *et al.* reported fewer bacterial infections in admissions with simple iron deficiency anaemia than in a dubious 'control' inpatient group with a variety of other causes of anaemia (megaloblastic and refractory), but they also reported more malaria in the iron-deficient patients (8/16 cases after initiation of therapy). Unfortunately, they did not give details of which patients were on oral or parenteral therapy or whether patients had received therapy before admission.⁶

The Murrays, in their report of the effects of iron treatment in Somali nomads (see below), also noted that nomads entering a feeding camp had no infections if they were iron-deficient ($n = 26$) in contrast with a high rate of infections in those with normal iron status (19/64).⁷

Evidence for a protective effect of low iron stores at birth on subsequent malarial experience was obtained in a prospective study conducted in Papua New Guinea (described in more detail below). Babies with lower birth haemoglobins were less likely to have malaria at field follow-up or to be admitted with malaria during the 1st year of life.^{8,9} Since birth haemoglobin is the main iron source during the 1st year of life, this effect may be evidence that iron deficiency protects from malaria.

In contrast, Snow and colleagues attempted

to see if measurement of iron status in 1-9-year-old Gambian children before the start of the malaria transmission season could predict malarial experience and morbidity during that season. They found no correlation between any measures of iron status and subsequent malarial experience in this older age-group.¹⁰

There are many differences in design between these two studies, but age is the major confounding difference. The younger immune naive infants appeared to show an advantage of low iron status while older semi-immune children did not.

Iron treatment

There is massive hyperferraemia following parenteral iron administration which lasts 2-3 days after intravenous¹¹ and up to 3 weeks following intramuscular iron dextran.¹² This effect is not seen with oral iron supplementation in normal doses,¹³ although gut intraluminal iron may be high. Circulating iron dextran complex may be a source of iron for bacterial growth immediately following injection when serum bacteriostatic action is lost. This is a particular danger during the neonatal period when such therapy is absolutely contraindicated.¹⁴

In the 1970s, several uncontrolled studies incriminated iron therapy in acute exacerbations of pre-existing or latent infections. In most of these reports parenteral iron was used. Byles and D'Sa, in an uncontrolled study, reported 11 cases of clinical malaria in 917 pregnant women immediately following parenteral iron therapy.¹⁵

Although the majority of the above adverse effects were associated with parenteral therapy, an important and often quoted study in the 1970s used oral iron. The Murrays, a family team, conducted a prospective, placebo-controlled, randomised trial of 30 days oral iron supplementation to 137 adult Somali nomads with iron deficiency anaemia.¹⁶ Iron treatment increased haemoglobin and transferrin saturation during the study. Although no malaria was noted at the start of the study in either group, 13 clini-

cal attacks of malaria occurred in the iron group ($n = 71$) and only one in the control group ($n = 66$) by the end of the trial; these attacks were presumed by the authors to be reactivations. Fevers were significantly commoner in the iron group. The study was single blind and follow-up was limited to the 30 days of treatment. The treatment group still had high reticulocyte counts and higher transferrin saturations than the control groups at the end of this period.

In all the above adverse reports, infections were noted shortly after commencement of iron therapy. It was thus clear that prospective long-term studies were needed to separate the effects of treatment from the effects of steady-state iron balance.

It was with these aims in view that a prospective, randomised, double-blind, placebo-controlled trial of iron supplementation in infancy was carried out in Papua New Guinea in the early 1980s.^{8, 9, 16, 17} It was established that iron deficiency was prevalent among infants in the study population. Malarial transmission was intense in the area. To avoid the known risks of iron therapy in the neonatal period¹⁸ a single dose of iron dextran (150 mg elemental iron) was administered to the treatment group (236) at 2 months of age; control infants (250) received an injection of sterile pyrogen-free saline. Infants were re-examined and relevant blood samples taken 1 week after the injection and at 6 and 12 months of age. All admissions of study children to hospital during the year were documented.

No differences in malaria rates were seen at the 1-week follow-up visit, but at both the 6- and 12-month visits there were differences in malaria slide positivity and spleen rates which were higher in the iron treatment group. The slide positivity rate associated with iron was 64% for each visit and spleen rates were 30-40% higher than controls. Twenty-five per cent of the iron treatment group had malaria-associated admissions to hospital in the 1st year of life compared with 17% of the placebo group ($p < 0.05$) but no effect of iron was noted on parasite densities.

A high birth haemoglobin was synergistic with the iron treatment on susceptibility to malaria. Infants who received iron *and* had a higher birth haemoglobin had a 40% risk of being admitted with evidence of malaria in the 1st year of life.

Although increased malaria rates were the most clearly demonstrable result of this study, clinical attacks of malaria were a relatively less common primary reason for admission than were acute lower respiratory infections (16% vs 63%). All 12 deaths in the study were due primarily to pneumonia. Rates of admission for pneumonia and duration of hospital stay were higher in the iron dextran group. In addition, infants with higher birth haemoglobins were significantly more likely to be admitted with pneumonia.⁹ Since these findings conflict with the results of all previously reported longitudinal studies in infants in non-malarious areas, the possibility that malaria might have had an effect on susceptibility to pneumonia was examined. Indirect evidence is available for this: 89% of pneumonia admissions had evidence of malaria (blood slide positive and/or significant splenomegaly), a much higher rate than that observed in the same cohort in the field. Support for this idea of an effect of malaria morbidity through its influence on pneumonia comes from a recent study in the same community.¹⁹ If a close interaction between malaria and pneumonia is substantiated, it will go a long way to explain the apparently opposite effects of iron supplementation on paediatric respiratory disease in temperate compared with tropical countries.

Several factors limit any general extrapolation from the findings in the New Guinea study for malarious areas. Firstly, a parenteral iron preparation was used and, secondly, the study group used was a cohort of infants aged 2 months who may be regarded as immunologically less mature than others in malaria-endemic areas. In contrast, in a more recent 16-week study in the same area, Harvey *et al.* showed no adverse effects of oral iron supplementation in pre-pubescent school children, particularly in relation to malaria indices. They speculate that immunity in their older

children may have masked the potential interaction between iron and malaria.²⁰

Another factor which needs to be taken into account in such intervention studies is the interaction between the different genotypes of globin chain disorders and the iron therapy. Oppenheimer *et al.* noted that the effect of parenteral iron on susceptibility to malaria was largely masked in children with single deletion α thalassaemia when compared with normals.²¹ Menendez and co-workers by contrast found in a placebo-controlled trial of oral iron to multi-gravidae that mothers with AS genotype (and their babies) showed deleterious effects while AA mothers benefited from iron.²² Since both these globin chain disorders themselves protect from malaria and reach very high polymorphic frequencies, such interactions must be taken into account.

A number of confounders may thus help to explain the apparently conflicting results of the ten or more iron intervention trials performed in the tropics since the mid-1980s on infants and children both with and without malarial and iron deficiency anaemia. Of these studies, two have shown deleterious effects of therapeutic doses of oral iron^{23, 24} on malarial experience, while another has shown that therapeutic doses of iron were associated with an increase in non-malarial infectious morbidity, particularly pneumonia in children during recovery from malaria, with no benefit on haemoglobin recovery.²⁵ All other trials show no malaria-related effects of oral iron supplementation,²⁶⁻²⁹ and variable haematological benefits, depending partly on the concurrent use and efficacy of antimalarials. In one of these latter studies, no increase in malaria rate was seen, but iron had no effect on haemoglobin levels in children with malaria. Schneider and co-workers describe this as malaria masking the benefit of iron.²⁹ A similar effect was seen in Oppenheimer's iron study, and two-way analysis-of-variance indicated that iron supplementation was associated with a greater degree of haemolysis due to malaria.⁸

The Tanzanian trial of Menendez *et al.* was similar to the previous New Guinea study⁸ in that an age cohort of infants was started on

2 mg/kg oral iron daily at 8 weeks of age for 16 weeks only and anti-malarial prophylaxis was varied. The theoretical advantages of this scheme were (i) that iron was given when rapid haemoglobin synthesis ensured maximal utilization of the iron, and (ii) that dynamic effects of supplementation on body iron compartments occurred in a period of maternal malarial protection and stopped before most infants were likely to contract their first dose of malaria. Iron supplementation had no significant effect on subsequent malarial experience but there was an overall benefit on haemoglobin levels. Respiratory disease rates were not reported.²⁸

All the other trials have used mixed age groups up to 14 years, and generally did not adjust for age in analysis. Smith *et al.* in The Gambia recruited children aged 6 months to 5 years with anaemia of various causes.²³ Iron deficiency was prevalent and may have included malaria. During the period of maximal malaria transmission, half received 3-6 mg/kg oral iron for 12 weeks and the other half placebo. Fever associated with high malarial parasitaemia was more frequent in the iron group, and at the end of the study spleen rates were higher in 2-year-olds treated with iron. Apart from age structure, other differences between this and the Menendez study were the higher dose of iron, the timing of iron therapy to coincide with malaria transmission and the low prevalence of α thalassaemia. The Gambia has an unusually low rate of deletion α thalassaemia (85% of the population have no deletions).^{23, 30} Generally in malaria-endemic parts of the continent, including East Africa (personal observation, unpublished), 50-70% of the population are heterozygous or homozygous for the deletion.³⁰ This might have resulted in deleterious effects of oral iron being more obvious in Smith's Gambian study.

Pregnancy

Women in their first pregnancies have peculiarly lowered immunity to malaria in endemic areas.³¹ In this context, it was noted in an

observational study in Papua New Guinea that treatment of anaemia in primigravidae with total dose iron infusion was with higher rates of maternal perinatal malaria but this effect was not seen in multiparae. After controlling for confounders and covariates, the parenteral iron had no net beneficial effect on haemoglobin in either group.³² Oral iron is a standard supplement in pregnancy, and in many parts of the tropics parenteral iron is often administered as presumptive treatment of anaemia during pregnancy. Since anaemia during pregnancy in the tropics is commonly due to malaria, treatment with iron may carry a risk to primigravidae and AS genotypes. Those groups of individuals with a high risk of anaemia secondary to malaria (infants, toddlers and mothers) are also selectively more likely to receive iron either as a supplement or as presumptive treatment for anaemia.

Iron withdrawal and malaria

With the clinical and experimental evidence for interactions between iron and malaria, two clinical trials of iron chelation in malaria were published recently. In the first, 28 asymptomatic parasitaemic volunteers had a significantly enhanced parasite clearance when given desferrioxamine B (DF) compared with randomised controls, but recrudescence was common.³³ In a randomised double-blind, placebo-controlled trial in Zambia, recovery time from deep coma was shortened by half by the addition of intravenous desferrioxamine to the standard quinine/fansidar treatment regime. In addition, rate of parasite clearance was twice as fast in the DF group.³⁴

Summary of clinical findings

1. Clinical states of *iron overload* may be associated with increased infections with splenectomy as an added risk factor. Desferrioxamine therapy in these conditions may reduce the incidence of some forms of sepsis but may increase the risk of *Yersinia* and fungal infections.
2. The possible beneficial relationship be-

tween *iron deficiency* and infectious susceptibility remains controversial and may depend on the type of organism and the age of the patient.

3. Oral *iron supplementation* has been associated with fewer respiratory infections in developed communities. With the appropriate choice of dose (not more than 2 mg/kg/day in under-5s), target population and timing (to avoid times of highest malarial risk), this intervention may be haematologically beneficial and may not exacerbate malaria in tropical areas.
4. *Iron treatment*, especially by the parenteral but also by the oral route, in doses greater than 2 mg/kg/day in under-5s has been associated with acute exacerbation of infection, particularly malaria and pneumonia, in the tropics. In the treatment of severe anaemia when malaria is or may be a cause, low efficacy of the concurrent malaria treatment may allow malarial interactions with therapeutic doses of iron.
5. Assessment of the effects of iron intervention on infectious morbidity in malarious areas should always take into account the interaction of malaria with morbidity due to respiratory infections.

Recommendations

Given the present incomplete knowledge of the interactions of iron and malaria, what recommendations can be given to health planners and paediatricians?

Iron dextran prophylaxis to infants in malarious areas (previously a common practice) is definitely contraindicated. Oral iron in infancy may also carry a risk if given in therapeutic doses at times of increased risk of malaria. Oral iron supplementation to older immune children may not be associated with adverse effects but further work is needed to confirm appropriate doses. In malarious areas, the practice of presumptive treatment of anaemia with parenteral iron should probably be contraindicated but further controlled clinical studies are needed before making definite recommendations.

Iron treatment for anaemia in a malarious area should be covered or preceded by effective antimalarial therapy. Iron therapy should be oral and where possible the decision to use iron should be based on laboratory evaluation of the cause of anaemia.

In the light of results from prospective, controlled clinical studies, policies for standard presumptive treatment of anaemia at the primary health care level in developing countries need to be reviewed, with particular reference to age, malarial endemicity, prevalence of globin chain disorders and other identifiable causes.

At present there is no good evidence that standard recommendations for oral iron supplementation and iron fortification of food-stuffs in childhood in developed countries could adversely affect susceptibility to infection.

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