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The immune response in iron-deficient young children: effect of iron supplementation on cell-mediated immunity

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Abstract. The effects of iron deficiency on immunity remain controversial. This study was designed to assess the impact of iron supplementation on the immune status, in 81 children aged 6 months–3 years, at high risk for iron deficiency, using a longitudinal double blind randomised and placebo-controlled study. Lymphocytes of iron-deficient children produced less interleukin-2 in vitro. Iron supplementation for 2 months increased mean corpuscular volume, serum ferritin and serum transferrin, but had no effect on the parameters of T-cell mediated immunity. The lower interleukin-2 levels in iron-deficient suggest that cell-mediated immunity may be impaired in iron deficiency.

Key words: Iron deficiency – Iron supplementation – Immune functions – Cell-mediated immunity – Interleukin-2

Introduction

It has been claimed that iron deficiency in children may impair immune capacity and resistance to infections [3, 12, 16, 19, 21, 28]. In spite of numerous studies, no firm conclusions have been reached [4, 5, 8–10, 27]. Clinically, some data suggest that iron deficiency predisposes to infection [1, 14]. Other studies support the opposite hypothesis, namely that iron deficiency protects against infection [24, 25].

Such controversial clinical data may be explained by the presence of other nutritional deficiencies, by variations in the definition of iron deficiency, by infections or other factors which may affect the immune response and in most studies, by the absence of a control group [6, 9, 14, 18]. To assess the impact of iron supplementation upon immune status, we performed a longitudinal double-blind randomised and placebo-controlled study in children at high risk for iron deficiency.

Subjects and methods

Probands were selected at random from a population of children aged 6 months–3 years undergoing a free systematic examination in four children's health centres from December 1989 to April 1990, in an area of Paris known for its low socio-economic level. Children: (1) with chronic disease; (2) who had an infection within the last 2 weeks; or (3) who had received iron or folic acid supplements within the 3 months preceding the study were excluded. Children presenting a haemoglobin level below 90 g/l were secondarily excluded. The study protocol was approved by the ethics committee of the Xavier Bichat Medical Faculty, Paris. Informed written consent was obtained from parents prior to participation. Anthropometric and prior vaccination data were obtained from the files of the health centres. Body composition was evaluated by the body mass index (weight/height^2) expressed as Z score for age [26]. Subjects were randomly assigned to one of two groups and received either placebo (P group) or iron (I group) for 2 months. Patients in I group weighing less than 11 kg received 30 mg and those over 11 kg, received 45 mg of elemental iron (oral hydroxyproline iron) daily. Compliance was evaluated by interview.

Seven millilitres of whole blood were withdrawn by venipuncture at the start of the study and after 2 months. Haemoglobin, haematocrit, red blood cell count, mean corpuscular volume and white cell count were measured on a Coulter Counter S 560 (Coultronics, France). The white cell differential was assessed by microscopic examination of blood smears after May-Grünwald-Giemsa staining. Erythrocyte protoporphyrin measurement was performed by haematofluorometry. Serum iron was assayed colorimetrically and serum ferritin by an enzyme-linked immunoabsorbent assay. Serum transferrin, C-reactive protein (CRP), orosomucoid, IgG, IgA and IgM were measured by nephelometry. Detailed procedures and percentage transferrin saturation calculation are described elsewhere [13]. Anaemia was defined according to WHO criteria [29], and iron deficiency by a combination of at least two abnormal values for the three following indicators: serum ferritin

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Abbreviations: CRP = C reactive protein; PBMC = peripheral blood mononuclear cells; PHA = phytohaemagglutinin A

level ≤ 12 µg/l, transferrin saturation ≤ 12%, and erythrocyte protoporphyrin concentration ≥ 3 µg/gHb. An isolated depletion of iron stores was defined by a low serum ferritin level (12 µg/l or less) without other abnormalities in iron parameters. An inflammatory process was considered to be present when the CRP concentration was above 12 mg/l and/or the orosomucoid level was above 1.4 g/l.

T-lymphocyte subsets were determined by fluorescence staining on freshly drawn blood. Monoclonal antibodies used were: anti CD3, anti CD4 and anti CD8 (Becton Dickinson). Fluorescence analysis was performed using a cytofluorograph FACStar plus (Becton Dickinson). Peripheral blood mononuclear cells (PBMC) were isolated from freshly drawn heparinised venous blood by means of Ficoll-Hypaque (Pharmacia) density gradient centrifugation. Proliferation assays were performed as described elsewhere [20]. Briefly, PBMC were stimulated either with mitogen in 3-day culture (phytohaemagglutinin; PHA Wellcome, final dilution 1/700) or with antigen (tetanus toxoid; Merieux, final dilution 1/ 250). To limit the amount of blood withdrawn, pooled human AB serum instead of autologous serum was used for culture. The blastic transformation of the T-lymphocytes was determined by evaluating [^{3}H]-thymidine incorporation with a beta scintillation counter (Delta 3000, Searle). To evaluate IL-2 production by activated T-lymphocytes, PBMC were isolated and cultured as previously described and stimulated by PHA (final dilution 1/1000) in a 2-day culture. IL-2 concentration was measured in the culture supernatants by radioimmunological assay (IL-2 RIA kit; Medgenix).

Data were analysed using SPSS computer programs (statistical package for the Social Sciences, SPSS Inc. Chicago). Differences between iron-deficient and non-iron-deficient groups, and between the P and I groups prior to supplementation were tested by Student's t-test and chi-square test. Differences before and after supplementation between P and I groups were tested by analysis of covariance, adjusting for the pre-treatment value of the dependent variable. Since serum ferritin, CRP and orosomucoid approach a log normal distribution, a log transformation of these parameters was used for all calculations; for IL-2, a square root transformation was used. Results are presented in original units. Statistical significance was established at a P value < 0.05.

Results

Data at onset of study

Eighty-one children were included in the study. Forty-nine (60.5%) had haemoglobin levels of less than 110 g/l and were considered as anaemic, and 53 children (65%) had iron deficiency. Seventeen of the non-iron-deficient children had an isolated depletion of iron stores according to our criteria. Iron-deficient and iron-sufficient children showed no differences in anthropometric and sociodemographic parameters (Table 1), except for the parity of mothers which was higher in the iron-deficient group (P < 0.02). Seventy-six (94%) of the children had received at least three injections of tetanous toxoid at the onset of the study. Inflammation-related parameters did not differ between the two groups (Table 2). Five out of 28 iron-sufficient children and 14 out of 53 iron-deficient children had laboratory signs of an inflammatory process. The production of IL-2 was significantly lower in the iron-deficient than in the iron-sufficient group (Table 3). This difference persisted after exclusion of children with laboratory signs of inflammation (P < 0.02). On the other hand, there were no differences between the two groups with respect to serum immunoglobulin levels (IgG, IgA, IgM), T-lymphocyte subsets (expressed in total number or as percentage) and in the response to PHA or tetanus toxoid.

Longitudinal data

Of the 81 children included in the study, 6 had a haemoglobin level of less than 90 g/l and were secondarily excluded from the protocol. Of the 75 children who remained, 40 were included in the P group and 35 in the I

Table 1. General and anthropometric data in iron-dificient and iron-sufficient children. Mean ± SD

	Iron-sufficient (n = 28)	Iron-sufficient (n = 53)	P value[a]
Age (months)	19.91 ± 8.82	17.09 ± 6.72	NS
Mother's parity	1.77 ± 0.88	2.70 ± 1.38	< 0.02
Birth weight (kg)	3.30 ± 0.51	3.29 ± 0.47	NS
Weight (kg)	11.42 ± 2.19	11.09 ± 1.98	NS
BMI (Z score)	–0.07 ± 1.20	0.09 ± 1.14	NS
Sex (males/females)[b]	15/13	22/31	NS
Ethnic origin (french/immigrant)[b]	8/20	10/43	

NS, Not significant
[a] Student's t-test
[b] Number of subjects

Table 2. Iron and inflammation-related parameters in iron-deficient and iron-sufficient children. Mean ± SD

	Iron-sufficient (n = 28)	Iron-sufficient (n = 53)	P value[a]
HB (g/l)	113.7 ± 8.7	104.7 ± 10.5	< 0.001
MCV (fl)	78.14 ± 5.59	72.43 ± 6.40	< 0.001
Serum iron (µmol/l)	13.35 ± 4.88	6.48 ± 2.65	< 0.001
Serum transferrin (g/l)	3.50 ± 0.54	3.92 ± 0.64	< 0.05
Transferrin saturation (%)	15.39 ± 6.37	6.86 ± 3.09	< 0.001
Erythrocyte protoporphyrin (µg/gHb)	2.37 ± 0.40	4.98 ± 3.71	< 0.001
Serum ferritin (µg/l)	10.03 ± 9.97	6.92 ± 10.93	
	5.10[b]	3.42[b]	NS
	3.70[b,c]	2.21[b,c]	< 0.05
CRP (mg/l)	4.12 ± 0.58	4.60 ± 2.33	NS
Orosomucoid (g/l)	1.00 ± 0.46	1.06 ± 0.45	NS
Leucocytges (cells/mm^3)	9900 ± 2780	11264 ± 3441	NS
Polymorphonuclear (cells/mm^3)	2286 ± 1327	2546 ± 1542	NS

NS, Not significant
[a] Student's t-test
[b] Geometric mean
[c] After exclusion of children with biological evidence of inflammation

Table 3. Serum immunoglobin, T-cells, lymphoblastic response and interleukin-2 in iron-deficient and iron-sufficient children. Mean ± SD

	Iron-sufficient ($n = 28$)	Iron-deficient ($n = 53$)	P value[a]
Serum immunoglobins (g/l)			
IgG	12.27 ± 4.08	14.62 ± 8.33	NS
IgM	0.91 ± 0.31	0.92 ± 0.29	NS
IgA	2.41 ± 0.73	2.75 ± 0.93	NS
T-cell subsets (% of lymphocytes)			
CD3+	64.70 ± 8.72	64.28 ± 8.99	NS
CD4+	40.69 ± 9.71	37.58 ± 11.06	NS
CD8+	23.69 ± 7.38	24.35 ± 10.30	NS
T-cell-subsets (cells/mm^3)			
CD3+	4433 ± 1631	5103 ± 2117	NS
CD4+	2755 ± 1138	2870 ± 1172	NS
CD8+	1650 ± 843	2000 ± 1352	NS
Proliferative response of lymphocytes[b]			
Stimulus			
none (day 3)	511 ± 411	485 ± 387	NS
PHA	33982 ± 16024	33156 ± 15384	NS
none (day 7)	631 ± 444	545 ± 450	NS
tetanus toxoid	13570 ± 11714	10644 ± 8681	NS
Interleukin-2 (U/ml)			
Stimulus			
none (day 2)	0.70 ± 0.66	0.76 ± 0.89	NS
PHA	11.33 ± 6.63	8.33 ± 5.58	< 0.05
PHA[c]	13.08 ± 6.31	9.02 ± 5.79	< 0.02
Stimulation index (% cpm/cpm)	1.7 ± 0.5	1.5 ± 0.4	< 0.05

NS, Not significant

[a] Student's t test

[b] ^{3}H thymidine uptake (cpm)

[c] Excluding children with biological evidence of inflammation

group. I and P groups were comparable in sociodemographic, anthropometric, physical and biological parameters. Two children in the P group and 3 children in the I group were lost to follow up.

At the end of the study period, mean corpuscular volume, serum transferrin and serum ferritin had improved in I group (Table 4). There was no effect of iron supplementation upon inflammation-related parameters (Table 4) or upon indicators of the immune status (Table 5).

Discussion

We found lower in vitro production of IL-2 by PHA activated lymphocytes in iron-deficient children. This suggests that iron deficiency may impair T-lymphocyte functions, but this finding is not confirmed by the data after supplementation. There was no reduction in the number of T-lymphocytes and T-subsets, and the blastic transformation tests with different antigens or mitogens were normal. The poor efficiency of iron supplementation in

Table 4. Iron and inflammation-related parameters in the placebo and the iron receiving groups before and after supplementation. Mean ± SD

	P group $n(1) = 40$ $n(2) = 38$	I group $n(1) = 35$ $n(2) = 32$	P value[a]
Hb (g/l)			
(1)	109.9 ± 8	109.3 ± 9.8	
(2)	110.6 ± 7.9	110.7 ± 10.1	NS
MCV (fl)			
(1)	75.38 ± 5.95	75.63 ± 5.37	
(2)	74.79 ± 6.05	76.34 ± 5.76	< 0.001
Serum iron (µmol/l)			
(1)	9.85 ± 5.21	8.47 ± 4.27	
(2)	10.19 ± 4.71	9.66 ± 5.03	NS
Serum transferrin (g/l)			
(1)	3.69 ± 0.63	3.79 ± 0.60	
(2)	3.84 ± 0.57	3.57 ± 0.57	< 0.05
Transferrin saturation (%)			
(1)	11.16 ± 7.09	9.18 ± 4.45	
(2)	10.89 ± 5.48	11.11 ± 6.07	NS
Erythrocyte protoporphyrin (µg/gHb)			
(1)	3.41 ± 2.48	3.55 ± 1.79	
(2)	3.17 ± 2.82	3.23 ± 1.70	NS
Serum ferritin (µg/l)			
(1)	7.00 ± 7.37	10.19 ± 13.83	
(2)	3.91 ± 7.78	6.51 ± 6.38	< 0.05
Geometric mean (1)	3.77	4.21	
Geometric mean (2)	1.70	3.61	
CRP (mg/l)			
(1)	4.84 ± 2.73	4.09 ± 0.51	
(2)	4.97 ± 5.83	4.61 ± 1.52	NS
Orosomucoid (g/l)			
(1)	1.09 ± 0.49	0.99 ± 0.39	
(2)	1.01 ± 0.86	0.87 ± 0.30	NS
Leucocytes (cells/mm^3)			
(1)	10865 ± 3368	10629 ± 3173	
(2)	10271 ± 2979	9653 ± 2519	NS
Polymorphonuclear (cells/mm^3)			
(1)	2507 ± 1455	2405 ± 1899	
(2)	2521 ± 10864	2515 ± 138	NS

(1) Value before supplementation; (2) value after supplementation; NS, not significant

[a] Effect of supplementation (analysis of covariance)

Means of I and P group supplementation did not differ significantly (Student's t-test)

Table 5. Serum immunoglobulin, T-cell subsets, lymphocyte proliferative response and interleukin-2 assays, in the placebo and the iron receiving groups, before and after supplementation. Mean ± SD

	P group *n* (1) = 40 *n* (2) = 38	I group *n* (1) = 35 *n* (2) = 32	*P* value[a]
Serum immunoglobulins			
IgG (g/l)			
(1)	14.47 ± 9.26	12.84 ± 4.30	
(2)	12.72 ± 3.30	12.32 ± 3.91	NS
IgA (g/l)			
(1)	0.92 ± 0.33	0.90 ± 0.25	
(2)	0.86 ± 0.27	0.85 ± 0.21	NS
IgM (g/l)			
(1)	2.65 ± 0.96	2.50 ± 0.69	
(2)	2.60 ± 0.87	2.84 ± 1.77	NS
T-cells subsets (% of lymphocytes)			
CD3+			
(1)	62.92 ± 9.45	66.50 ± 7.84	
(2)	65.21 ± 7.63	68.25 ± 8.56	NS
CD4+			
(1)	37.43 ± 11.62	40.50 ± 9.40	
(2)	39.24 ± 9.11	41.84 ± 10.39	NS
CD8+			
(1)	23.92 ± 9.62	24.79 ± 9.84	
(2)	24.24 ± 7.33	23.66 ± 6.86	NS
T-cells subsets (cells/mm^3)			
CD3+			
(1)	4899 ± 2329	5096 ± 1612	
(2)	4651 ± 1852	4437 ± 1640	NS
CD4+			
(1)	2766 ± 1269	3060 ± 1038	
(2)	2808 ± 1245	2749 ± 1240	NS
CD8+			
(1)	1939 ± 1372	1927 ± 1092	
(2)	1750 ± 963	1516 ± 685	NS
Proliferative response of lymphocytes[b]			
Stimulus			
none (day 3)			
(1)	561 ± 432	428 ± 363	
(2)	609 ± 588	485 ± 369	NS
PHA			
(1)	34002 ± 15546	32882 ± 15732	
(2)	33389 ± 12351	35028 ± 10645	NS
none (day 7)			
(1)	551 ± 324	624 ± 580	
(2)	535 ± 542	525 ± 518	
tetanus toxoid			
(1)	12372 ± 15555	13556 ± 11043	
(2)	13138 ± 9947	11196 ± 7666	NS

Table 5 (continued)

	P group *n* (1) = 40 *n* (2) = 38	I group *n* (1) = 35 *n* (2) = 32	*P* value[a]
Interleukin-2 (U/ml)			
Stimulus			
none (day 3)			
(1)	0.69 ± 0.90	0.82 ± 0.74	
(2)	1.11 ± 1.01	0.69 ± 0.70	NS
PHA			
(1)	10.49 ± 6.24	7.76 ± 5.04	
(2)	10.57 ± 6.55	9.99 ± 5.34	NS

(1) Value before supplementation; (2) value after supplementation; NS, not significant

[a] Effect of supplementation (analysis of covariance)

[b] ^{3}H thymidine uptake (cpm)

Means of I and P group supplementation did not differ significantly (Student's *t*-test)

terms of its effect on immune parameters, and especially upon IL-2 production, may be explained by irregular or inadequate compliance with iron supplementation, by the degree of iron deficiency, the brevity of the supplementation period (only 2 months) and the small number of children included in the study. Thus we cannot impute the impairment of IL-2 production to iron deficiency with certainty because this study did not allow us to exclude the existence of other associated nutritional deficits.

In our group of children considered as non-iron-deficient, there was a high prevalence of isolated depletion of iron stores (61%). A possible prejudicial effect of iron store depletion upon the immune response could mask eventual differences existing in the group of children with optimal iron status. This could thus explain our finding of impaired IL-2 production without impairment of lymphocyte subsets and blastic lymphocyte transformation tests, which is in contrast to other reports [7, 11, 16, 17, 21, 28]. Alteration of cell division by impairment of ribonucleotide reductase (an iron-dependent enzyme) has previously been described in iron deficiency and could be one of the hypotheses to explain these perturbations in cell-mediated immunity [15]. Since IL-2 production was evaluated in vitro on a constant lymphocyte number, the absence of a decrease in the circulating CD4 + lymphocyte rate in iron-deficient children found in our study, contrary to that of Berger et al. [3], suggests the existence of a qualitative alteration in T-lymphocyte functions, rather than quantitative abnormalities.

Transferrin is known to play an essential role in the maintenance of growth of continuous cell lines and is an essentiel component of serum-free media for cell culture [2]. The mechanisms by which transferrin exerts its effect on growing cells are not yet known [23]. Mainou Fowler and Brock showed, in an animal model [22], that the concentration of iron bound to transferrin in the culture medium is an important factor in optimum lymphocyte proliferation. They established that the in vitro re-

sponse to concanavalin A of lymphocytes is impaired primarily when the serum used in the culture medium contains very low levels of transferrin-bound iron. In the same way, in the literature, the use of autologous sera of iron-deficient subjects in the culture medium led to perturbations in lymphoblastic transformation tests [11], but the use of heterologous sera gave contradictory results [17]. Thus, it could partly explain why, in our study in which we used heterologous serum (for ethical reasons), we found impairment only of the production of IL-2 and not of the lymphocyte blastogenic response. The latter depends directly upon the capacity of production of IL-2 by the T-cells and is probably a less sensitive parameter. To support this hypothesis, it would be useful to compare the production of IL-2 in iron-deficient and iron-sufficient children using culture media containing either autologous or heterologous sera.

Neckers and Cossman [23] suggested the role of transferrin and its receptor in the immune response by demonstrating the existence of an interdependence of receptors for IL-2 and for transferrin. Thus, we could expect that the affinity of its receptor for low saturated transferrin would be decreased [4]. Because of the interdependence of the expression of the transferrin and the IL-2 receptors, the latter hypothesis may be one explanation for the decrease in the production of IL-2 which we found in our study in the group of iron-deficient children and, perhaps, for the impairment of the cellular immune response previously reported [7, 11, 16, 17, 21, 28]. This study, however, did not enable us to reach a conclusion concerning consequences of iron deficiency upon other immune indicators. Confirmation of our findings by other experimental, clinical and epidemiological studies may elucidate previous controversial reports and lead to the proposal for a coherent clinical and public health approach when dealing with populations known to be at risk for iron deficiency.

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