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Nutrition

Effects of iron therapy on blood lead concentrations in infants

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ABSTRACT

To determine whether blood lead concentration is elevated in iron-deficient infants, blood lead and serum ferritin concentrations, serum iron/transferring iron-binding capacity (Fe/TIBC) and complete blood counts were measured in 30 iron deficient and 35 control infants, aged 6–24 months. All 30 iron-deficient infants received iron supplementation (ferric hydroxide-polymaltose complex, 6 mg/kg Fe^{3+}/day) for 1–6 months. Blood lead concentrations were measured in 18 of the iron deficient infants after their ferritin levels returned to the normal range. The geometric mean blood lead concentration was higher in iron deficient than in control infants (1.846 vs. 1.416 μg/dL). After iron therapy, the blood lead levels of iron-deficient infants decreased significantly compared with pre-treatment levels (1.785 vs. 2.386 μg/dL), and the hemoglobin and ferritin concentrations increased significantly. These findings indicate that iron deficiency increases blood lead concentrations in infants with very low blood lead concentrations.

Introduction

Iron deficiency affects approximately one-third of the world's population [1]. This condition most often occurs in infants aged between 6 months and 3 years, due to rapid growth and inadequate dietary intake of iron [2]. Iron-deficiency anemia has been associated with poor cognitive development, poor motor development and behavioral problems [3,4].

Because iron is absorbed via mechanisms similar to those of other divalent metal ions, including manganese and lead, a dietary deficiency in iron can lead to excess absorption of lead, a widespread toxicant with detrimental effects on health. This has serious health implications, given that lead from environmental and/or occupational sources can enter the body via inhalation or ingestion [5], and that evidence has emerged that lead neurotoxicity occurs in children at lower levels of lead exposure than had been previously thought [6]. Indeed, iron deficiency has been found to predispose animals to lead toxicity by increasing gastrointestinal lead absorption [7–9]. Several studies have suggested an association between iron status and blood lead concentration in children [10–19], whereas other studies have disputed this association [20–25]. These conflicting results prompted the present longitudinal study on iron-deficient infants treated with iron supplements. We assessed whether blood lead concentrations are higher in iron-deficient than in control infants, and whether treatment of the former with iron supplements decreases lead concentrations.

Subjects and methods

Subjects

Thirty infants with iron deficiency (serum ferritin concentration < 15 μg/L), ranging in age from 6 months to 2 years, were selected from infants being treated at an ambulatory pediatric hematology clinic at Ulsan University Hospital, South Korea. Thirty-five age- and sex-matched control subjects, who were healthy and had serum ferritin concentrations higher than 15 μg/L, were selected from among the infants visiting a general pediatric clinic in the same hospital. Subjects were excluded if they were delivered preterm or at low birth weight; had a history of any disease, or concurrent acute or chronic infection or inflammation; or if their parents had a history of occupational exposure to lead. All 30 iron-deficient infants were treated with ferric hydroxide–polymaltose complex (6 mg/kg Fe^{3+}/day) for 1–6 months (Mean ± SD, 2.9 ± 1.5 months). Blood lead concentrations were determined in all control subjects and in all iron-deficient subjects prior to iron supplementation. Blood lead concentrations were assessed again in 18 of the iron-deficient infants after their ferritin concentrations returned to the normal range. Twelve were lost to follow up. Parents of infants in both groups provided written informed consent, and the study

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protocol was approved by the institutional review board of Ulsan University Hospital.

Laboratory testing

A questionnaire was administered to the parents of each infant to obtain basic perinatal information, along with information on breast feeding and nutrition. Heparinized venous blood samples were obtained from each infant, and blood count, hemoglobin concentration, hematocrit, serum ferritin concentration, and serum iron/transferring iron-binding capacity (Fe/TIBC) were measured. Iron deficiency was defined as serum ferritin < 15 μg/L [26].

Lead determination in whole blood

Blood lead concentration was determined by flameless graphite furnace atomic absorption spectrophotometry (AAS) (Spectra AA880-GTA 100, Varian, Australia) using the standard addition method. Briefly, aliquots (0.1 mL) of blood were diluted 20 fold with 0.1% (v/v) Triton X-100, and 15-μL samples were injected into the graphite furnace. All blood lead analyses were carried out in the Ulsan University Hospital laboratory, which had passed the Quality Assurance Program (for lead) operated by the Korea Occupational Safety and Health Agency. For internal quality assurance and control, commercial reference materials were used (Lyphochek1 Whole Blood Metals Control; Bio-Rad). The limit of detection for blood lead concentration using this method was 0.6 μg/dL. No tested blood sample had a lead concentration below the limit of detection.

Statistical analyses

Blood lead concentrations were natural log-transformed because their distributions were skewed, and their geometric means (GMs) were calculated. Significant differences in the means of continuous variables between iron-deficient and control infants were determined using Student's *t*-tests. Differences in the proportion of male infants between these groups were determined using the chi-square test. Significant differences in the means of variables before and after iron therapy were determined using paired *t* tests. SPSS (v14) software was used for all statistical analyses, and a *P* value <0.05 was considered significant.

Results

Age and gender distribution did not differ between the iron-deficient and control groups. The iron-deficient infants had a higher GM blood lead concentration than controls (1.846 vs. 1.416 μg/dL). In addition, hemoglobin concentrations, hematocrit levels, and serum ferritin levels differed significantly in the two groups (Table 1).

Mean duration of breast feeding was longer in iron-deficient than in control infants. All the iron-deficient infants were treated with an iron supplement, and 18 were tested again for blood lead concentrations after their ferritin concentrations reached normal range. The mean blood lead concentration in these 18 infants was significantly lower after ferric hydroxide treatment compared to before such treatment (2.386 vs. 1.785 μg/dL), while their hemoglobin, ferritin, and Fe/TIBC (%) levels were significantly higher after treatment (Table 2). However, in 4 of these 18 infants, ferric hydroxide treatment was not accompanied by a decrease in blood lead levels.

Discussion

The present longitudinal study of iron-deficient infants receiving iron supplements showed that iron deficiency was associated with increased blood lead concentrations, in good agreement with previous findings [10–19]. Most of those studies, however, were cross-sectional and could not determine whether iron deficiency preceded lead exposure or vice versa.

Few previous studies have assessed the temporal relationship between iron deficiency and increased blood lead [11,15,19]. A longitudinal study showed an association between iron deficiency and high blood lead level in young children, with blood lead levels ranging from <5 μg/dL to 40 μg/dL [15]. Another study, in children aged 10–15 years, found that mean blood lead levels were 6.9 μg/dL in iron deficient and 4.3 μg/dL in control children, and that iron

Table 1
Demographic, clinical and laboratory features of the study subjects.

Group characteristics	Iron-deficient infants (*n* = 30)	Control (*n* = 35)	*P* value
Age (months)	11.9 ± 3.7	11.7 ± 4.0	0.820
Male (%)	70.0	51.4	0.128
Breast feeding (months)	10.3 ± 3.4	6.3 ± 4.9	<0.001
Lead (μg/dL)*	1.846 (0.65–4.26)	1.416 (0.32–3.60)	0.026
Hemoglobin (g/dL)	10.45 ± 1.87	11.85 ± 1.02	0.001
Hematocrit (%)	32.62 ± 4.15	35.08 ± 2.61	0.007
Ferritin (μg/L)*	7.43 ± 3.04	39.10 ± 23.78	<0.001
Fe (μg/dL)	38.83 ± 30.35	47.00 ± 28.20	0.269
TIBC (μg/dL)	410.93 ± 53.56	353.35 ± 46.85	<0.001
Fe/TIBC (%)	10.2 ± 8.9	13.6 ± 8.6	0.121

Results reported as mean ± SD, except for *geometric mean (range).

Table 2
Laboratory features of iron-deficient infants before and after iron therapy.

Group characteristics	Before iron therapy (*n* = 18)	After iron therapy (*n* = 18)	*P* value
Lead (μg/dL)	2.386 (1.130–4.710)	1.785 (1.150–3.990)	0.008
Hemoglobin (g/dL)	10.40 ± 1.75	12.38 ± 0.88	0.001
Hematocrit (%)	32.57 ± 3.81	36.95 ± 2.28	0.002
Ferritin (μg/L)*	7.21 ± 3.15	21.28 ± 6.96	<0.001
Fe (μg/dL)	35.39 ± 26.00	65.00 ± 37.64	0.009
TIBC (μg/dL)	416.78 ± 47.84	366.17 ± 54.31	<0.001
Fe/TIBC (%)	8.89 ± 7.0	18.0 ± 9.7	0.002

Results reported as mean ± SD or *geometric mean (range) and compared by paired *t* tests. Iron-deficient infants were followed-up after 1–6 months (mean ± SD, 2.9 ± 1.5 months) of treatment with ferric hydroxide-polymaltose complex (6 mg/kg Fe^{3+} per day).

supplementation significantly decreased blood lead concentrations in the former group [11]. A clinical trial assessing the impact of iron supplementation on blood lead concentrations in infants with iron deficiency found that changes in blood lead concentrations corresponded closely to changes in iron status [19]. The mean blood lead level in 165 iron-deficient Costa Rican infants before iron treatment was 10.98 μg/dL (SEM 0.26), ranging from 5.8 to 36.9 μg/dL, with 57.6% (95/165) having lead levels >10 μg/dL [15].

In contrast to the works described above, other studies have found no association between iron deficiency and increased blood lead concentrations [20–25,27]. This discrepancy may be due in part to differences in the age distribution of study subjects, the assumptions used, or lead exposure levels. For example, no association was observed in studies in which the study subjects was comprised of older female children or adolescents [17,20,22]. Postmenarche adolescents do not show an association between high blood lead and iron deficiency due to the overshadowing of the effects of estrogen. Moreover, studies have found that iron and lead concentrations are not correlated in the absence of iron deficiency [23,24]. For example, a randomized, placebo controlled trial found that reductions in blood lead were similar in iron and placebo treated groups of Mexican children [23]. Thus, iron supplementation reduces blood lead concentration in anemic, but not in non-anemic, children.

In addition, studies showing correlations between lead and iron concentrations [12,16,17] have typically been performed in children exposed to high environmental levels of lead levels, with blood lead levels of 20–40 μg/dL, whereas studies reporting no association [21,25] were performed in children with lower blood lead levels (11.0 and 11.4 μg/dL). However, longitudinal studies of children with blood lead levels in the similar range have shown an association between iron status and blood lead concentration in children following iron supplementation [11,15,19]. Compared to these previous longitudinal studies, the blood lead levels in the control and iron deficient groups in the present study (1.416–1.846 μg/dL) were much lower. Thus, in contrast to previous findings, we observed an association between iron supplementation and blood lead in infants with very low blood lead concentrations. Paradoxically, one study found that lead levels were not correlated with iron status in children with severe lead poisoning (mean blood lead 86 μg/dL; range 63–190 μg/dL) [27]. Thus, the increase in lead associated with iron deficiency appeared to be overshadowed by severe lead poisoning.

Our results suggest that increased blood lead levels are associated with prolonged breast feeding, a risk factor for iron deficiency in infants [28,29]. Infants given prolonged breast feeding tend to be iron deficient, and thus have higher blood lead levels. However, not all infants who received prolonged breast feeding were iron deficient in the present study. This may be due to variations in the iron status of infants depending on whether they receive iron-rich supplementary food during prolonged breast feeding. Lead is ubiquitous in the environment. Factors influencing blood lead concentrations in an infant after iron treatment include exogenous environmental lead exposure and blood lead levels in the mother, which were not evaluated in the present study.

The present findings have several public health implications. First, they emphasize the importance of assessing iron and hematologic status when addressing environmental exposure to lead and related neurobehavioral effects in infants. Due to the high prevalence of iron deficiency in children, epidemiological observations with iron deficiency as a susceptibility factor should be considered, especially when assessing health risks associated with exposure to low levels of environmental lead. Second, the risks of long-lasting and possibly permanent mental and psychomotor impairment associated with elevated blood lead levels [6], as well as from the iron deficiency itself [3], make the prevention of iron deficiency a very important public health concern. Third, both increased blood lead levels and prolonged breast feeding, which is also a risk factor for iron deficiency, were observed in anemic infants in the present study. Our results suggest that babies who are breast-fed for prolonged periods should be given plain, iron-fortified cereals or other good sources of dietary iron.

The present study had several limitations. In regard to the method used to measure iron concentration, serum ferritin is an acute-phase reactant that may be artificially elevated in the presence of inflammation [30], a potential confounding factor that we did not rule out (e.g., by adjusting for C-reactive protein, which was not measured). We did, however, exclude infants with acute or chronic inflammation or infection. In addition, we did not measure blood lead concentration in the mothers of these infants or current exogenous environmental lead exposure. Lead levels in an infant's blood may be influenced by those in the mother's blood or by environmental lead exposure, as well as by iron deficiency.

In conclusion, we have shown here that iron deficiency increases blood lead concentrations in infants with very low blood lead concentrations.

Conflict of interest

The authors declare that there are no conflicts of interest.

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