Effect of Iron Therapy on Behavior Performance in Nonanemic, Iron-Deficient Infants

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ABSTRACT. In an effort to determine whether iron deficiency, in the absence of anemia (hemoglobin >11.0 g/dL), might produce alterations in behavioral development, four groups of nonanemic infants, 9 to 12 months of age, with varying degrees of iron deficiency were studied. Infants were classified as iron sufficient, iron depleted, or iron deficient based on measurements of serum ferritin concentration, erythrocyte protoporphyrin values, and the mean cell volume of erythrocytes. Subjects in each group were tested with the Bayley Mental Development Index, treated with parenteral iron, and retested seven days later. The administration of iron produced a significant increase in the Mental Development Index scores (+21.6 points) in the infants with iron deficiency but no significant change in the scores of infants with iron sufficiency (+6.2 points) or only iron depletion (+5.6 points). It is concluded that iron deficiency, even in the absence of anemia, results in biochemical alterations that impair behavior in infants. *Pediatrics* 1983;71:877–880; *iron deficiency, behavior, Bayley Scales of Mental Development.*

Previously we reported[1] that treatment of infants with iron deficiency anemia produced a significant improvement in behavior as measured by the Bayley Mental Development Index. The use of parenteral iron produced the effect within 1 week of administration.

We now wish to report our findings that indicate that iron deficiency, in the absence of anemia, is also associated with impaired test performance in infants who are 9 to 12 months of age. Treatment of iron-deficient infants with parenteral iron produced a significant increase in scores after 1 week of therapy.

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MATERIALS AND METHODS

All healthy infants, 9 to 12 months of age, attending the Pediatric Clinic of the State University Hospital, were tested for evidence of iron deficiency. Capillary blood was obtained for measurement of hemoglobin, red blood cell indices, and levels of erythrocyte protoporphyrin and serum ferritin.

Hemoglobin and red cell indices were determined by electronic counting (Coulter counter, model S-Plus, Coulter Electronics, Hollywood, FL); erythrocyte protoporphyrin was measured in a front-faced fluorometer[2]; serum ferritin concentration was measured in duplicate employing a radioimmunoassay.[3]

Only subjects in whom the hemoglobin concentration was greater than 11.0 g/dL were considered nonanemic[4] and eligible for study. Subjects qualifying for further study were then classified into four groups based on the laboratory test results. Subjects were classified as iron sufficient, iron depleted, or with iron-deficient erythropoiesis based on cellular and/or biochemical evidence of iron deficiency (Table 1).[5]

Subjects in group 3 were judged to have biochemical evidence of iron deficiency as reflected by an increase in the erythrocyte porphyrin concentration whereas subjects in group 4 displayed both biochemical and cellular evidence of iron deficiency in that the increased erythrocyte porphyrin was accompanied by a decrease in the mean cell volume (MCV) of the red cells.

Subjects with a history of premature birth, neonatal distress, chronic illness, or congenital anom-

alies were excluded from further study.

Following the initial screening and classification, subjects were invited to return for further testing and therapy. All subjects were tested within 2 weeks of the initial screening procedure. Attempts were made in groups 1, 2, and 3 to match patients for sex and color.

At the return visit infants were administered the Bayley Scales of Mental Development[6] and the Bayley Infant Behavior Record was completed. Following the testing session all subjects received 50 mg of iron as 1 mL of iron-dextran (Imferon, Merrill-National Laboratories, Cincinnati) by intramuscular injection. In subjects with an increased concentration of erythrocyte protoporphyrin, blood samples were obtained for the determination of blood lead.

Exactly seven days after the initial testing session, the subjects returned for a second administration of the Bayley Scales of Mental Development. All the Bayley tests were administered by the same psychologist (A.S.H.) who had no knowledge of the iron status classification of the subjects.

Following the second testing session, all of the initial laboratory screening procedures were repeated.

Changes of scores within groups were analyzed using the paired t test. Changes in score between groups were analyzed by the unpaired t test. The χ^2 test was used to examine the significance of changes in score of 10 points or more.

This experimental protocol was approved by the Institutional Committee for the Protection of Human Subjects. The Committee prohibited the use of a placebo treatment group.

RESULTS

A total of 306 infants were initially screened. Of this group, 25 (8.2%) were found to have iron-deficiency anemia with a hemoglobin concentration of less than 11.0 g/dL, and were excluded from further study. Sixty-one percent of the patients were normal, 16.1% were iron depleted, 8.2% were iron deficient, and 7.5% were not classifiable.

A group of 38 infants participated in the study and completed the two psychological testing sessions. All patients in the study underwent blood lead determinations and all had levels less than 17 μg/dL.

The initial laboratory findings and the sex, race, and mean age of the subjects in the four study groups are shown in Table 2. The mean hemoglobin concentration of subjects in group 4 was found to be significantly lower ($P = .01$) than that of subjects in group 2, although all infants in group 4 had hemoglobin values in excess of 11.0 g/dL.

Following iron therapy all infants had serum ferritin levels well within the normal range. The serum ferritin values for the four groups averaged 68.1, 54.6, 69.6, and 79.4 ng/mL, respectively.

The initial scores of the Bayley Mental Development Index, the scores on the retest following

TABLE 1. Classification of Subjects into Four Groups Based on Laboratory Findings

Group	Laboratory Finding			
	Hemoglobin (g/dL)	Ferritin (ng/mL)	Erythrocyte Porphyrin (μg/dL)	Mean Corpuscular Volume (fL)
1. Normal	≥11.0	>12.0	<30	≥70
2. Iron depleted	≥11.0	<12.0	<30	≥70
3. Iron deficient (biochemical)	≥11.0	<12.0	>30	≥70
4. Iron deficient (biochemical and cellular)	>11.0	<12.0	>30	<70

TABLE 2. Characteristics of Four Study Groups*

	1: Normal (n = 10)	2: Iron Depleted (n = 10)	3: Iron Deficient (n = 10)	4: Iron Deficient (n = 8)
Age (mo)	10.7 ± 0.7	11.0 ± 0.8	11.0 ± 0.8	11.4 ± 0.9
Sex: M/F	5/5	5/5	5/5	4/4
Color: B/W	6/4	6/4	6/4	4/4
Hemoglobin (g/dL)	11.9 ± 0.4 (11.0–12.6)	12.7 ± 0.4 (11.7–13.3)	11.9 ± 0.5 (11.2–13.1)	11.3 ± 0.4 (11.0–12.7)
Ferritin (ng/mL)	31.2 ± 16.6 (14.0–49.2)	10.4 ± 1.4 (7.8–12.0)	10.2 ± 1.3 (8.8–11.9)	9.8 ± 2.0 (6.6–11.9)
Erythrocyte porphyrin (μg/dL)	20.4 ± 6.9 (8–29)	17.5 ± 7.5 (8–29)	40.6 ± 11.3 (32–60)	41.8 ± 7.1 (33–55)
Mean corpuscular volume (fL)	77.3 ± 3.6 (74–84)	75.9 ± 3.0 (70–80)	74.7 ± 1.9 (73–79)	68.3 ± 1.8 (64–69)

* Values are means ± SD; range is shown in parentheses.

TABLE 3. Mental Development Index Scores Before and After Iron Therapy*

Group	Before	After	Change
1. Normal (n = 10)	90.8 ± 18.2	97.0 ± 20.9	6.2 ± 6.0
2. Iron depleted (n = 10)	94.6 ± 25.2	100.2 ± 26.8	5.6 ± 4.5
3. Iron deficient (n = 10)	83.9 ± 21.1	104.0 ± 15.3	20.1 ± 13.1†
4. Iron deficient (n = 8)	85.5 ± 17.3	109.1 ± 15.7	23.6 ± 11.2†
1 and 2 (n = 20)	93.7 ± 21.3	98.6 ± 23.4	5.9 ± 5.5
3 and 4 (n = 18)	84.6 ± 19.0	106.3 ± 15.3	21.6 ± 12.1†

* Values are means ± 1 SD.
† $P < .01$.

TABLE 4. Subjects with Increase in Mental Development Index Score of at Least 10 Points

Group	No. of Subjects/Total
1. Normal	3/10
2. Iron depleted	1/10
3. Iron deficient	6/10
4. Iron deficient	8/8
1 and 2 (non-iron deficient)	4/20
3 and 4 (iron deficient)	14/18

iron therapy, and the changes in score are shown in Table 3. Although the initial scores of the iron-sufficient control subjects and the iron-depleted infants, groups 1 and 2, were somewhat higher than those of the infants in the iron-deficient groups, groups 3 and 4, the differences failed to achieve statistical significance ($P = .175$).

Following iron therapy, the scores in both of the iron-deficient groups increased significantly ($P < .01$) whereas there was no significant change in score in either the iron-sufficient (group 1) or iron-depleted infants (group 2). When groups 1 and 2 were combined, the mean increase in score in the test-retest was 5.9 points whereas the mean increase in groups 3 and 4 was 21.6 ($P < .01$).

Following iron therapy the mean Bayley scores of infants who were initially iron deficient (groups 3 and 4) were somewhat higher than the mean scores of infants in groups 1 and 2, but these differences did not achieve statistical significance ($P = .2$).

In view of the fact that some child psychologists fail to attach much importance to test-retest scores that fail to change by as much as 10 points, the number of infants in each group with changes in score of at least 10 points was separately examined (Table 4). When the non-iron-deficient infants (groups 1 and 2) were compared with the iron-deficient infants (groups 3 and 4) by χ^2 analysis, a highly significant difference was observed ($P < .001$) with 14/18 infants in groups 3 and 4 displaying an increase in score of at least 10 points as contrasted with only 4/20 in groups 1 and 2.

DISCUSSION

The finding that treatment of iron deficiency results in a rapid improvement in the developmental scores of infants confirms and extends our previous observation.[1] In the original study the administration of parenteral iron to infants with mild iron deficiency, mean hemoglobin of 8.73 g/dL, produced a significant increase in the scores of the Bayley Mental Development Index in an average of seven days. The present study suggests that the correction of iron deficiency, rather than the treatment of anemia, is responsible for the improved developmental performance of the infants.

Previous studies in animals[7-9] as well as in infants and young children[10-14] have suggested a relationship between iron deficiency and alterations in performance. Many of the human studies have been judged to be inconclusive[15] as a result of flaws in study design.

Most recently, Lozoff and co-workers[16] described the results of study of Guatamalan infants, 6 to 24 months of age, with and without mild iron deficiency anemia. The mean pretreatment score on the Bayley Mental Development Index, the same test instrument employed in our study, was found to be significantly lower in the anemic group. In a double-blind randomized study, six to eight days of oral iron therapy did not reverse the deficit. We are unable to explain the discrepancy in the treatment results between our observation of a response with intramuscular iron and the lack of response with oral iron. It is possible that saturation of the biochemical processes underlying the behavioral abnormality is more rapidly achieved with the use of parenteral iron.

The failure to find any behavioral deficit in the iron-depleted, but not as yet iron-deficient infants, is consistent with the report of Dienard and coworkers.[17] They were unable to observe any differences in attending behavior and cognitive development between nonanemic infants with normal or reduced serum ferritin concentrations.

Analysis of individual items on the Bayley Mental Development Index or the Bayley Infant Behavior Record failed to disclose any consistent improvement in any particular test item that might have been responsible for the overall improvement in score. Other investigators[10,12] have suggested that

correction of attentional and processing deficits may be responsible for the differences in scores between iron-deficient and iron-sufficient subjects. An improvement in attention and the processing of stimuli would produce a global improvement in score and might not be attributable to any particular test item. Unfortunately, there is no standardized, widely accepted test that measures these processes in infants 9 to 12 months of age.

On the basis of present knowledge, it is unclear what serves as the biochemical basis that links iron deficiency to behavioral alterations. The metabolism of a variety of putative neurotransmittors has been found to be altered in iron-deficient animals and man. Monoamine oxidase activity was observed to be decreased in the liver, heart, and adrenal gland of iron-deficient rats[18] and in the platelets of humans.[19] Urinary excretion of norepinephrine is increased in iron-deficient rats[20] and in children.[21] The brain of iron-deficient rats has been found to have reduced aldehyde oxidase activity, an enzyme that plays a central role in the degradation of serotonin. Serotonin levels have been found to be increased in iron-deficient rats.[22] Catecholamines or serotonin remain possible candidates for the explanation of alterations in behavior in iron deficiency.

If others can confirm our results and demonstrate the reversible nature of the behavioral abnormalities associated with iron deficiency, the societal implications are obvious as well as enormous. Studies conducted as part of the National Health and Nutrition Examination Survey indicate that as many as 35% of infants, primarily in the lower socioeconomic groups, are iron deficient.[23] Iron deficiency may have significant implications in terms of learning and ultimate scholastic performance[13] for many members of our society.

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