NUTRITION AND THE LIFE CYCLE

DEVELOPMENTAL AND BEHAVIORAL EFFECTS OF IRON DEFICIENCY ANEMIA IN INFANTS

BASED ON THE 1997 AVANELLE KIRKSEY LECTURE PRESENTED BY BETSY LOZOFF AT PURDUE UNIVERSITY

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This paper shows that iron deficiency anemia in infancy is a serious nutritional disorder with long-lasting consequences for behavioral development. Evidence is provided from studies on rats that iron deficiency during gestation or early postnatal life directly effects the brain, and early neurophysiologic data in humans also indicate a direct effect on the central nervous system.

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Lack of dietary iron is probably the most prevalent nutritional deficiency in developed and underdeveloped countries alike. Using data from more than 500 studies in different countries, De Maeyer and Adiels-Tegman[1] calculated that 20% of adult men, 35% of adult women, and 40% of children worldwide are anemic. Half of the anemia is thought to be related to iron deficiency.[1,2] Infants are at even higher risk because of their rapid growth and limited dietary sources of iron. Although only a few studies include prevalence data for infants, it is estimated that 25% of the world's infant population has iron deficiency anemia,[3] and many more have iron deficiency without anemia. In the United States, iron deficiency anemia in infants has declined dramatically in recent years in parallel with changes in infant feeding practices (such as increased breast-feeding and use of iron-fortified formulae and cereal, *etc.*). However, anemia is still common in some ethnic groups such as Alaskan Natives, African Americans, and Native Americans.[4]

ASSESSING IRON NUTRITIONAL STATUS AND IRON DEFICIENCY ANEMIA

Iron nutritional status (Table 1) is considered normal or iron-sufficient if normal values are obtained for hemoglobin (Hb) and for two, or preferably three, of the following measures of iron status: biochemical [serum ferritin, transferrin saturation, erythrocyte protoporphyrin (FEP)] or cellular [mean corpuscular volume (MCV)]. Iron depletion refers to depleted iron stores as indicated by a low serum ferritin level as the sole abnormality. Iron deficiency without anemia (*ie,* iron-deficient erythropoiesis) is defined by two or three abnormal iron measures even though Hb is still in the normal range. Iron deficiency anemia is defined as an Hb level (or hematocrit level) below reference levels (generally >2 standard deviations) and accompanied by at least two or three other abnormal iron measures.

A diagnosis of iron deficiency based on a single biochemical measure is limited, because each of the above measurements reflects different aspects of iron metabolism. Because conditions other than iron deficiency can affect each of these measures, the most conservative diagnosis is obtained with a minimum of three values. A positive hematologic response to iron therapy (*ie*, a rise in Hb of ≥1 g/dl[8]) is the most definitive of available standards, and it has been used as a criterion for defining iron deficiency.[9]

Although anemia is defined in relation to a reference Hb level, there are no universally used Hb standards, and indeed, Hb levels vary with age, sex, and location. An example of the latter is the increase in Hb levels at higher altitudes: in the Costa Rican study described below, the elevation of 1185 meters adds approximately 4 g/L to the reference Hb. Comparison between clinical studies can be particularly difficult when the reference ranges are not reported.[2]

ASSESSING BEHAVIOR AND DEVELOPMENT: OVERVIEW

Seven studies that included a careful definition of iron status and an appropriate comparison group assessed behavior and development in infants with iron deficiency anemia (Table 2). All of these studies used at least three measures to determine iron status in addition to hemoglobin or hematocrit and the presence or absence of anemia. Most used a standardized test of infant development, the Bayley Scales of Infant Development, to assess developmental behavior.[15]

The Bayley Scales have three components: a mental scale [mental developmental index (MDI)], motor scale [psychomotor developmental index (PDI)], and an infant behavior record (IBR). The widely used MDI is designed to assess sensory-perceptual activities and discriminations and the ability to respond to these, the early acquisition of "object constancy" and memory, learning and problem-solving abilities, vocalizations, and the start of verbal communication. The equally well accepted PDI gives a measure of gross and fine motor coordination and motor skills.

Some of the studies used Bayley's IBR in addition to the MDI and PDI. The IBR has 30 items that assess general behavior areas including affect, task orientation, and motor coordination, modes of sensory interest, and other areas such as judgment of adequacy of the test, evaluation of the child, assessment of play, and object attachment.

LINKING IRON DEFICIENCY ANEMIA TO DEVELOPMENTAL BEHAVIOR

Providing convincing evidence ("proof") that iron deficiency anemia in infancy actually causes a developmental problem is difficult. It depends on first establishing a reliable association between the two variables and then confirming that iron deficiency anemia occurs before the behavior deficit, and finally, proving that the relationship between iron deficiency anemia and behavior is real, *ie*, cannot be explained by another factor.[16,9] The first and last associations will be discussed here in relation to studies cited in Table 2; the second will be discussed later.

In all seven studies (Table 2), initial behavioral testing (*ie*, before iron therapy) showed lower mental test scores for iron-deficient anemic infants than infants with better iron status. In studies that measured MDI,[3,7,10–14] test scores were from 6 to 13 points lower. Five[7,10,12–14] of the seven studies also reported lower motor scores (9–14 points lower) for iron-deficient anemic children. In one of these studies[7] and two other earlier studies,[5,17] infants with a lesser degree of iron deficiency (*ie*, iron deficiency without anemia) did not have lower test scores.

Thus, the association between iron deficiency anemia

Table 1. Iron sufficiency and iron deficiency categories for infants

Group	Anemia	Hb (g/L)	Ferritin (μg/L)	Saturation (%)	FEP[a] (μg/dL)	MCV (fL)
Normal (iron-sufficient)	No	≥110	≥12	≥10	≤30	≥70
Iron-depleted	No	≥110	<12	≥10	≤30	≥70
Iron-deficient	No	≥110	<12	<10	>30	≥70
Iron-deficient anemic	Yes	<110	<12	<10	>30	<70

Adapted from Oski et al.[5] and Parks and Wharton[6].

[a]FEP cut off is approximately 30 μg/dL for whole blood or 100 μg/dL for packed cells. The prevalence of anemia for a given population is determined by definition of the normal Hb range and will vary with the cut-off values used. Actual values used in different studies may vary from those given above; the cut-off range is more rigorously defined in some (eg, Lozoff et al.[7] used ≤10.5 g/dL as cut-off for anemia); the studies cited in the present paper all specified their cut-off range.

Table 2. Developmental test scores for infants with iron deficiency anemia

Study (reference)	Location	Lowering of Bayley Infant Development scores[a] MDI[a]	PDI[a]	Iron therapy
10	Guatemala	13	9	6–8 days
11	Chile	12	n.s.	10 days
12	United Kingdom	⇓ social	⇓ fine motor[b]	Short term
7	Costa Rica	8	10	3 months
13	Chile	6–7	9–11	3 months
14	Indonesia	13	14	4 months
3	Costa Rica	6	n.s.	6 months

[a]Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores in this table represent the average number of points scored by the iron-deficient anemic infants below the average scores of comparison groups (infants with better iron status).
[b]Although the Grindulis et al. study[12] was not designed specifically to assess psychomotor development, infants were scored with a developmental test (the Sheridan Developmental Sequence)[6].

and lower developmental test scores is convincing. Investigators in other countries, working with different populations have been able to replicate the results that show that iron deficiency anemia is associated with altered infant behavior, producing clinically and statistically significantly lower mental and motor test scores.

Researchers hoped to get evidence that iron deficiency anemia actually causes the lowering of test scores by use of iron therapy to correct the differences. Convincing evidence for a causal relationship would be increases in MDI and PDI of formerly iron-deficient anemic infants, or at least among those whose iron status was corrected by iron therapy. Comparison of data in the available treatment studies is complicated by different lengths of treatment, differences in ages, and extent of iron deficiency anemia of infants when treatment began, in most cases the lack of a placebo group, for ethical reasons, and in others also the lack of nonanemic control group.

Earlier investigations adopted a short-term treatment (Table 2) similar to that used in the initial study of Oski and Honig[18] in which a significant increase in the MDI of 14 points was demonstrated after a 5 to 10 day period of iron therapy. This suggested that iron treatment could have a rapid effect on the behavior of iron-deficient anemic infants; however, the findings were misleading. The increase of 6 points in placebo test group scores was not significantly different from the increase for the iron-treated group. Furthermore, the study did not include a nonanemic control group for comparison. No subsequent short-term study has found an improvement in test scores that could be attributed to iron therapy.

Studying the effects of short-term iron therapy (7–10 days) seemed important from another perspective. This might allow an estimate of the effect of iron on brain before a marked hematologic effect could occur. Thus, iron-dependent neurotransmitters could be assessed before other systemic effects, such as oxygen-carrying capacity. The more clinically significant question, however, is: Can lower test scores of iron-deficient anemic infants be corrected with a routine course (2–3 months) of iron therapy? Using this paradigm, only one[14] of five studies showed a significant improvement of MDI test scores after a full course of treatment of iron deficiency anemia. Even in a study using a long course of iron treatment (6 months), test scores were not improved.[3] Hence, with a single exception, none of the full treatment studies has shown test score correction for the majority of iron-deficient anemic infants.

The lack of a statistically significant improvement in mental and motor test scores of most iron-deficient anemic infants after iron therapy means that the conclusion that iron deficiency anemia caused the behavioral alterations cannot be made with certainty. However, it is of interest that there was a significant increase in the motor test scores of a subset of infants (36% of the entire anemic group) whose iron deficiency anemia was completely corrected after 3 months of iron therapy.

Further evaluation of data from Chile and Costa Rica indicated that initial severity and chronicity of the iron deficiency in the anemic infants may explain their continuing lower test scores. For example, Walter and colleagues[13,19] were able to compare infants who had anemia for longer than 3 months with others whose iron deficiency anemia was of shorter duration. They found significantly lower test scores for the infants who had iron deficiency anemia for the longer period.

IN-DEPTH STUDIES OF IRON DEFICIENCY ANEMIC INFANTS IN COSTA RICA

Central and South America, with a high prevalence of iron deficiency, have been the location for several investigations. At the time of these studies, infant formula and cereals were not fortified, and there were no national or community programs of iron supplementation. Furthermore, the communities studied were relatively homogeneous, with no widespread anemia from parasites, malaria, hookworm, or hemoglobinopathies. The general standard of nutrition was good, and lead levels were low.

Studies of iron-deficient anemic infants from periurban lower middle-class communities in the outskirts of San Jose, Costa Rica, provide further information relevant to the enigmas facing clinical researchers, and, in particular to the relation between iron deficiency anemia and poorer developmental scores.[3,7] In a 1987 study,[7] 191 12- to 23-month-old infants were identified by door-to-door screening. This is preferable to recruiting children who are brought to a clinic, because this would bias the study with a population for whom the parents were already concerned. The medical history of each infant was reviewed, and only those free from medical conditions that could have influenced their hematologic status or behavior were invited to participate. Thirteen criteria were used, including no major congenital abnormalities, no iron therapy after 6 months of age, no major acute or chronic illness, birth weight ≥2.5 kg, and being born fullterm. The last two are essential, because preterm and/or underweight infants have a problem maintaining optimal iron nutrition after the first 2 postnatal months.[20] In all these studies, participants had normal physical exams and were free from acute or chronic illnesses. However, infants differed in their iron status: Hb levels ranged from anemic (≤105 g/L) to intermediate (106–119 g/L) to nonanemic (≥120 g/L). The nonanemic group contained iron-sufficient, iron-depleted, and iron-deficient subgroups, and infants in the anemic and intermediate groups were all iron deficient according to the above definitions (see Fig. 1 and Table 1).[7]

Results of the initial Bayley Infant Development evaluations for MDI and PDI for the 1987 study[7] are shown in Figure 1. Moderately anemic infants were the only group that differed statistically from others in mental development; this difference is given in Table 2. For motor development, both moderately and mildly anemic groups had statistically significantly lower test scores. These groups were combined and compared with the rest of the sample (Table 2). MDI and PDI Bayley Test scores of the different iron status groups after 3 months of iron therapy closely resemble those in Figure 1, showing persistence of lower scores. However, a subset of anemic infants did not end treatment with lower scores. The MDI and PDI test scores for these infants, who were iron sufficient at the end of 3 months of treatment, are compared in Figure 2. As mentioned above, 3-month iron therapy corrected anemia in all children but corrected iron deficiency completely in only a minority of anemic infants (27% of the moderate and 50% of the mild groups). Even though the improvement in MDI test scores of these infants was nonsignificant when compared with iron-sufficient infants, the 10-point improvement in the PDI scores for these infants was significant.[7]

In the 1987 Costa Rican study, administration of iron was done largely by project personnel who went to houses and put the medication into the children's mouths. All infants responded to the iron, 100% of the anemic group corrected their anemia, and the average increase in hemoglobin was almost 4 g/L.[3,7] These results demonstrated that the infants not only received the iron, but that their bodies used it, and most importantly, that their anemia was caused by iron deficiency. Yet the lack of test score improvement in the majority of anemic infants was puzzling. To test the possibility that longer treatment was needed, a later study used the same age group and criteria and reassessed infants after 6 months of iron therapy. The MDI test scores in 32 anemic infants compared with 54 nonanemic controls were significantly lower before treatment, and this difference persisted even after 6 months of iron treatment. The PDI test scores, however, were not significantly different at any stage of the study.[3]

LONG-TERM EFFECTS OF IRON DEFICIENCY ANEMIA IN INFANCY

One of the limitations of the Bayley Scales of Infant Development is their inability to predict later development.[19] For this reason, the children in the 1987 study[7] were reassessed when they were 5 years of age; among the original 191 infants, 163 (85%) were available for testing. At 5 years of age, children were comparable on the nutritional measures assessed, irrespective of whether they were iron sufficient in infancy and whether or not they had received iron therapy. The children's iron status, as well as their general nutritional status (as reflected in growth), was excellent and comparable to that of US children of similar age.[21]

Results of the reevaluation followed the same pattern illustrated in the pretreatment MDI test scores (Figure 1). Moderately anemic infants who had remained iron-deficient after the initial study had significantly lower mental and motor scores than those who had experienced lesser

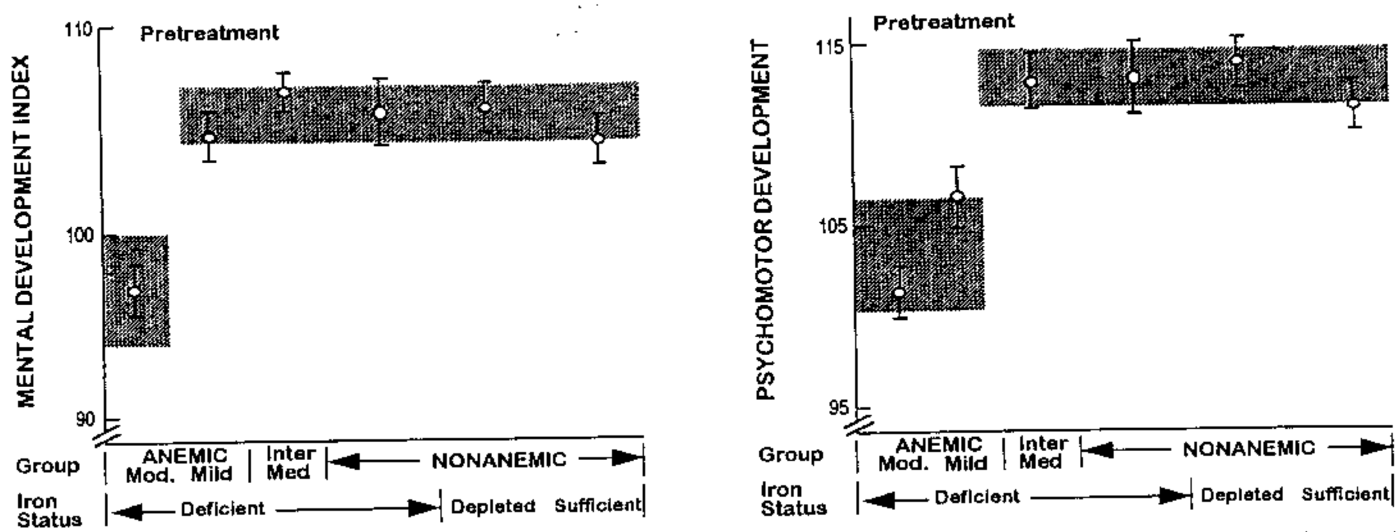

Figure 1. Pretreatment MDI and PDI scores at different levels of iron deficiency anemia. The hemoglobin levels used in this study ranged from anemic (≤10.5 g/dL; $n = 52$) to intermediate (10.6–11.9 g/dL; $n = 21$) to nonanemic (>12; $n = 94$); the anemic group was further subdivided into a moderately (≤10 g/dL; $n = 34$) and mildly (10.1–10.5 g/dL; $n = 18$) anemic group, and the nonanemic group contained normal or iron-sufficient ($n = 35$), iron-depleted ($n = 38$), and nonanemic iron-deficient subgroups ($n = 21$). Pretreatment MDI (left) and PDI (right) scores are age-adjusted means; the mean MDI score of moderately anemic group (96.6 ± 1.9) was significantly lower than that of other groups (combined mean, 104.6 ± 0.9; $p = 0.0002$); for the PDI scores, the moderately and mildly anemic group did not differ significantly; the mean PDI of the anemic groups (103.0 ± 2.2) varied significantly from that of the nonanemic groups (113.0 ± 1.3; $p = 0.0001$); the hatched area represents 95% confidence intervals. Reprinted by permission of PEDIATRICS, Vol 79, Page 981–995, 1987.

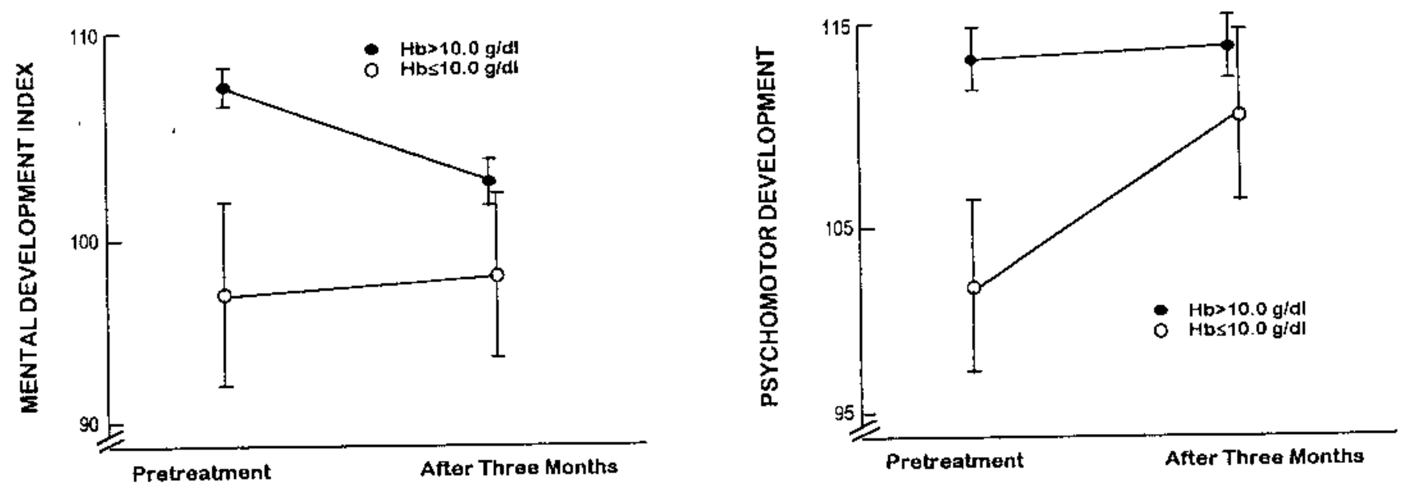

Figure 2. MDI and PDI scores for iron sufficient infants after 3 months of iron therapy. The mental (left) and psychomotor (right) scores are age-adjusted means ± standard error of the mean (SEM) and represent only infants who were iron sufficient after the 3 months of iron treatment. The formerly moderately anemic group (Hb ≤ 10 g/dL) whose MDI had been significantly lower (see Fig. 1) now had a mean MDI score (97.3 ± 4.2; $n = 9$) similar to infants previously with Hb >10 g/dL (101.9 ± 1.2; $n = 100$; $p = 0.30$). Improvement in anemic infants was nonsignificant ($p = 0.76$) in contrast to significant decrease in scores of other infants. In contrast to the MDI, the PDI of the formerly anemic infants (Hb ≤ 10.5 g/dL; $n = 17$) increased substantially and was comparable to that of the control group (Hb > 10.5 g/dL; $n = 90$; 110.2 ± 3.7 vs 114.4 ± 1.5; $p = 0.30$); however, the score of the control group showed no significant change. Reprinted by permission of PEDIATRICS, Vol 79, Pages 981–995, 1987.

degrees of iron deficiency, irrespective of the type of test. Their performance was statistically significantly lower in the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) Performance IQ (95.8 ± 11.8 vs 105.4 ± 11.3; $p < 0.001$) and remained so (99.0 ± 11.5 vs 104.8 ± 10.2; $p < 0.05$) after multiple regression analyses were used to control for differences in background characteristics (discussed below). The full-scale WPPSI IQ was also significantly lower (97.0 ± 13.1 vs 104.8 ± 11.2 in the rest of the sample; $p < 0.01$); however, after the adjustment for additional factors, it was not ($p = 0.13$). Test scores of fine and gross motor functioning, visual motor integration, quantitative concepts, and visual matching evaluations were significantly lower (Fig. 3).[21]

In addition, the data show that infants with higher hemoglobin levels who remained iron deficient after 3

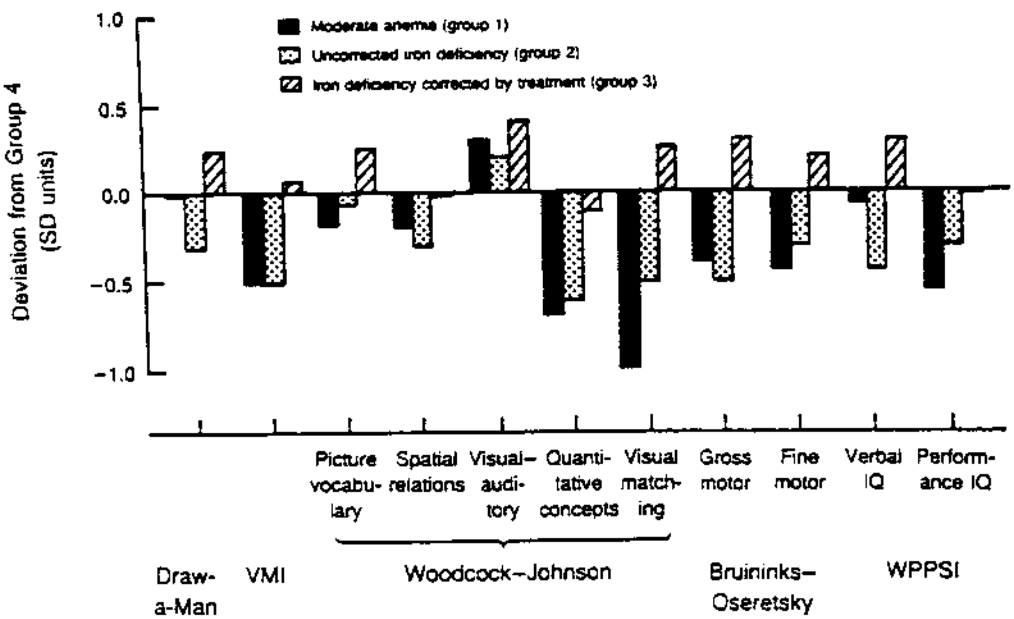

Figure 3. Long-term test differences based on iron status before and after infancy iron therapy. The comparisons are expressed in terms of adjusted mean standard deviation from the results of the reference group (group 4), which consists of the children who had good iron status before and after iron therapy; the means were adjusted for background characteristics using analysis of covariance. Group 1 (solid bar) was the group with moderate anemia in infancy, group 2 (dotted bar) had iron deficiency before and after treatment, and group 3 (hatched bars) had iron deficiency that was corrected. Draw-a-Man is a Goodenough-Harris Test, VMI is the Beery Developmental Test of Visual-Motor Integration, Woodcock-Johnson is a Psycho-Educational Battery, Bruininks-Oseretsky is a test of Motor Proficiency, and the WPPSI is the Wechsler Preschool and Primary Scale of Intelligence IQ tests as cited in Lozoff et al.[21] Reprinted with permission from Lozoff et al.[21]

months of iron therapy appeared to be equally at risk at 5 years of age. Their test scores were as low as those of children who had moderate iron deficiency anemia. Both groups had severe or chronic iron deficiency in infancy, in spite of the fact that their anemia was subsequently corrected. The 5-year study reinforces the earlier findings based on the Bayley Test scores and provides evidence about the significance of iron deficiency anemia in infancy. Even more alarming are data of the recently completed 12-year follow-up. Formerly iron-deficient children continue to perform at a lower level despite the fact that their iron status was normal. These children tested lower in reading, writing, and arithmetic (*ie,* in all basic learning skills) as well as in overall motor scores, indicating that iron deficiency anemia in infancy relates to long-lasting differences that affect the lives of children.[22]

Conceptual Model for Developmental Effects of Early Iron Deficiency Anemia

To provide a conceptual framework for how iron deficiency anemia might contribute to long-term disadvantage, both biologic and environmental mechanisms operating during development must be considered (Fig. 4).[23] Evidence for the importance of environmental factors is given below. In summary, infants born into disadvantaged homes—perhaps with limited resources—frequently suffer from poorer feeding practices and develop iron deficiency (or other nutrient deficiencies). Maternal depression and other stressors are frequently associated with poverty, and these, in turn, affect parenting and the overall support provided to children. The child's learning experiences are less than adequate, resulting in negative outcomes.

The biologic evidence is mainly from laboratory experiments with rats. These have demonstrated not only a decrease in iron concentration in brain when iron deficiency anemia occurs in early development, but also impaired myelination and neurotransmitter dysfunction, particularly in the dopamine system.[24–27] These changes would predictably lead to alterations in the maturation or function of a variety of aspects of the central nervous system. These changes could contribute to an altered behavior pattern, which might also affect the behavior of those rearing the child. As a result of iron deficiency anemia, infants may invite fewer learning experiences, which, over time, contributes to functional isolation:

- Changes in the affect or activity of an infant leads it to seek and/or receive less stimulation from the physical and social environment.
- Over time, this interferes with the normal acquisition of environmental information

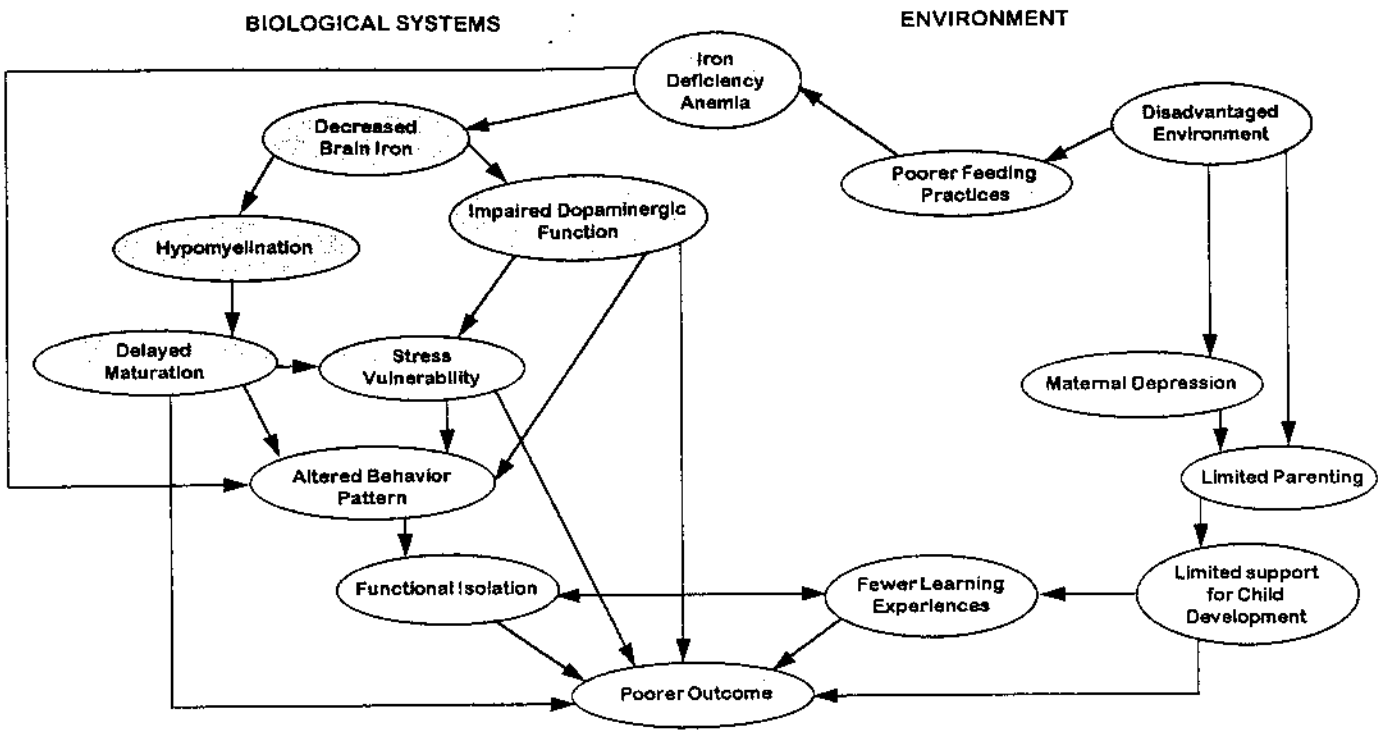

Figure 4. Conceptual model for developmental effects of early iron deficiency anemia. The right side of the model focuses on environmental influences on the child, and the left side begins with biologic influences. Both environmental and biologic mechanisms are shown to produce a poorer outcome.

This functional isolation contributes to poorer social, emotional, mental, and motor development

FUNCTIONAL ISOLATION

Functional isolation is a concept derived from the malnutrition literature. Alterations in an infant's emotional and energy levels influence the caregiving environment and, in this mutually interactive situation, eventually leads to poorer development and outcomes in a variety of psychologic, physical, and mental domains. Information suggesting that functional isolation applies to iron-deficient anemic infants comes from an analysis of the Bayley IBR and coding of behavior from videotape.

In the Costa Rican studies,[3,9,28] analysis of the IBR indicated abnormalities in affect in iron-deficient anemic infants before iron therapy. The behavior of the infants was also rated from videotapes. Independent observers rated iron-deficient anemic infants as more wary, with over a quarter of them being hesitant throughout the entire motor test. In contrast, only 10% of the infants with better iron status had similar behavior. Overall, anemic infants were rated as unusually fearful and unhappy, and more of them seemed to be excessively wary or hesitant with the examiner, more withdrawn, and easily tired or tense. These, together with similar findings from work in Guatemala[29,30] and Chile,[11,13,19] corroborate the concept of functional isolation, suggesting that the hesitant, withdrawn behavior of infants with iron deficiency anemia may limit their ability to learn from new and unfamiliar situations.

Another area in which behavioral differences were found related to the spatial relationship between mother and baby.[23,28,30] According to attachment theory, one of the most important social emotional phenomena during infancy is the development of an attachment relationship that is a secure base for exploring the world. An infant not only maintains close contact with the mother but also uses her as an anchor from which to explore the world, first beyond arm's length as a toddler, and then further as a preschooler, and further still, until eventually, the offspring leaves home. Proximity for an infant was defined in terms of close contact (*ie,* being within an arm's length), or distant (*ie,* beyond arm's length). Observations of proximity suggested that the iron-deficient anemic infants differed from nonanemic infants in being more likely to stay in close contact during their play behavior and motor testing, initiating more body contact. Their mothers spent less time at a distance from them, were less likely to break close contact, and were more likely to reestablish close contact if the infant moved away. Close contact is hypothesized to be a manifestation of disturbance in effect, or activity, perhaps because these infants are more fearful or because they have less energy. Again, this is evidence that these infants seek less stimulation and experience functional isolation.[23,28,30]

ENVIRONMENTAL CONTRIBUTION TO LOWER TEST SCORES

The other area of potential difference found when anemic infants were compared with those of better iron status was their immediate caregiving environment. More information about the families might help to understand the lower test scores of anemic infants. To evaluate cognitive stimulation in the home, the Caldwell-Bradley Home Inventory was performed.[31] In addition, the infant's nutritional status and feeding history (*ie,* the length of breast-feeding and the amount of cow milk consumed), and characteristics were assessed, such as sex, gestational age, birth weight and order, length, head circumference and other growth indicators, maternal age at child's birth, mother's education and IQ, father's IQ and presence in the home, and grandparents' presence in the home. With these more detailed measures, Lozoff et al.[3,7,9,28] found that anemic children were breast-fed for a shorter period of time, their mothers had low IQ scores, and the environment was less stimulating.

Mental and motor test scores were analyzed controlling for environmental factors. Test score results and behavioral differences were statistically significant after controlling for measures identified by the evaluation of environmental factors; these are the results cited in this paper. Nonetheless, the reality of children's lives is that their nutrient deficiency occurs in a context of a disadvantaged environment. The statistical manipulations done to control for the effects of environment are in fact a distortion of the reality of these children's lives. The dilemma is this: because iron deficiency occurs in less advantaged environments, and, as shown in four of the five studies that had a full course of treatment, iron treatment does not correct the lower test scores, how can one be certain that lower test scores are due to iron deficiency anemia, rather than some environmental factor(s)?

> ***Iron-deficient anemic infants are disadvantaged with respect to breast-feeding and family background.***

NEW INFORMATION ON IRON AND THE BRAIN

Rat studies have been invaluable in providing direct information on the effects of early iron deficiency anemia on the central nervous system. Questions relating to the central nervous system have been impossible to answer in the developing human infant. As mentioned above, animal studies have indicated a deficit in brain iron content, hypomyelination, and impaired dopaminergic function. The rat model may shed light on human infant iron deficiency anemia, because postnatal vulnerability of rat brain to nutritional and other environmental factors during neurologic development parallels that of humans. Furthermore, iron is distributed in similar brain regions and achieves maximal levels in a similar developmental pattern in both species.

Iron deficiency anemia in pregnant rats leads to iron deficiency anemia in the pups. Irrespective of timing and severity of the induced dietary anemia, developing rats have a 20 to 35% decrease in total nonheme (*ie,* not associated with hemoglobin) iron concentration in brain that is not corrected by iron therapy. Earlier studies started treatment after weaning; however, more recently, Felt and Lozoff[27] found that treatment at younger stages was also unsuccessful.

In these experiments,[27] mild iron deficiency anemia was induced in dams during four periods: early and late gestation and early and late lactation. Then, after a short anemic period, dams were treated to correct the anemia. Iron concentration in brains of their progeny was measured at 3 months. Iron deficiency imposed in dams during lactation significantly lowered iron concentration in brains of pups compared with a deficiency induced during gestation (21% lower). However, maternal iron treatment even in early gestation did not correct the iron deficit in brains of pups. This is particularly striking, because the dams were no longer anemic, and growth of pups was normal at birth. In both the gestation and lactation groups, brain iron concentration of pups at 3 months in the experimental groups was 15 to 33% lower than in controls. Thus, even with mild and quickly corrected anemia, the effects on brains of pups were long-lasting.[27]

The rat model has also been useful in examining the effects of iron deficiency anemia on behavior. In the Felt and Lozoff study,[26] all groups had behavioral alterations when compared with controls on a home orientation test (a sensitive indicator of early neural development) screened on postnatal days 8 and 12. Groups that were anemic at delivery had significant differences in behavior at 3 months, which included greater swim distance in the Morris water maze, and less defecation in an open field. Overall, there were fewer behavioral differences at 3 months of age, but changes may reflect subtle though persisting differences in arousal threshold and ability to use cues and learn from the environment to solve problems. Similar to the biochemical findings on brain iron concentration, the behavioral results suggest the importance of a normal iron level or iron sufficiency throughout the course of the crucial period of neural development.

HUMAN NEUROPHYSIOLOGIC DATA

Perhaps the most exciting new direction is the increased capacity to obtain direct data on the human brain. With the use of a sophisticated neurophysiology unit, colleagues of Lozoff[32] in Chile have obtained convincing evidence that iron deficiency anemia in infancy affects the developing central nervous system. In auditory evoked potential studies, 6-month-old iron-deficient anemic infants had a slower central conduction time (*eg,* longer nerve conduction latency) than did nonanemic controls. After 6 months of treatment, the difference increased, and it was even bigger at 18 months after a full year of treatment. This finding is particularly significant, because the normal increase in nerve conduction speed correlates with the process of myelination in the auditory pathway. The alterations observed would be compatible with an impairment in myelination. In other words, this is not only the very first direct and specific evidence of a central nervous system dysfunction in the human infant, but it is also documentation of the failure of iron treatment to correct it. At this stage, the study cannot determine whether this dysfunction is an arrest in development or an irregular progression.[32]

CONCLUSION

Iron deficiency is common, probably the most common nutrient deficiency, and its effects can be long-lasting. Even though many questions are unanswered, and many facets of the data are puzzling, iron deficiency anemia in infancy identifies children who are at long-lasting developmental and behavioral risk. There is now evidence for direct central nervous system changes, *eg,* nerve conduction time in the developing brain of iron-deficient anemic infants. Iron deficiency anemia in infancy can be prevented, and this seems to be the safest course if children are to achieve their full developmental and behavioral potential.

ADDITIONAL AUTHOR BIO'S

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