Effect of iron-deficiency anemia on cognitive skills and neuromaturation in infancy and childhood

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Abstract

Iron-deficiency anemia in infancy has been consistently shown to negatively influence performance in tests of psychomotor development. In most studies of short-term follow-up, lower scores did not improve with iron therapy, despite complete hematologic replenishment.

The negative impact on psychomotor development of iron-deficiency anemia (IDA) in infancy has been well documented in more than a dozen studies during the last two decades. Two studies will be presented here to further support this assertion. Additionally, we will present some data referring to longer follow-up at 5 and 10 years as well as data concerning recent descriptions of the neurologic derangements that may underlie these behavioral effects.

To evaluate whether these deficits may revert after long-term observation, a cohort of infants was re-evaluated at 5 and 10 years of age. Two studies have examined children aged 5 years who had anemia as infants using comparable tools of cognitive development showing persisting and consistent important disadvantages in those who were formerly anemic. These tests were better predictors of future achievement than psychomotor scores. These children were again examined at 10 years and showed lower school achievement and poorer fine-hand movements. Studies of neurologic maturation in a new cohort of infants aged 6 months included auditory brain stem responses and naptime 18-lead sleep studies. The central conduction time of the auditory brain stem responses was slower at 6, 12, and 18 months and at 4 years, despite iron therapy beginning at 6 months. During the sleep-wakefulness cycle, heart-rate variability—a developmental expression of the autonomic nervous system—was less mature in anemic infants. The proposed mechanisms are altered auditory-nerve and vagal-nerve myelination, respectively, as iron is required for normal myelin synthesis.

Key words: Iron deficiency, anemia, behavior, developmental neurology

Behavioral studies

When IDA ensues during the first 2 years of life, it is associated with delayed psychomotor development and changes in behavior. These effects have been shown to persist after several months of iron therapy, despite complete correction of iron nutrition measures. Moreover, it is still uncertain after an extended period of observation whether or to what extent these derangements are reversible. It is worrisome that the long-term prospective follow-up studies reported to date, to be discussed below, show the persistence of cognitive deficits at 5 to 6 and at 10 years of age in those who experienced IDA during infancy.

The inherent difficulties of identifying intervening variables in the complex field of mental development, coupled in some cases with suboptimal design, have prevented significant progress in the investigation of iron deficiency. However, two studies—one conducted in Costa Rica in 1982 [1], and the other in Santiago, Chile, in 1986 [2]—confirm conclusions arising from previous work.

The study in Santiago was performed in association with a field trial of fortified infant foods. A total of 196 healthy, full-term infants were assessed with the Bayley Scales of Infant Development (BSID) [3] at 12 (see Box 1), 12½, and 15 months of age. This well-known and accepted tool is used to determine psychomotor development from ages 3–42 months. It consists of a mental scale to evaluate cognitive skills, such as language acquisition and abstract thinking, and a motor or psychomotor scale to evaluate gross motor abilities, such as coordination, body balance, and

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Box 1. Bayley Scales of Infant Development

» Psychomotor development of the infant
» Mental development index (MDI)
» Psychomotor development index (PDI)
» Adjustment for the age 100 ± 16 (like the IQ)
» Behavior scale: psychologic evaluation

walking. These scales are expressed as an index adjusted for age as the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). In addition, it includes an Infant Behavior Record, which is based on clinical evaluation by a psychologist.

The Costa Rican study [1] enrolled 191 otherwise healthy 12- to 23-month-old infants with heterogeneous iron status. The infants were divided into groups ranging from most to least iron deficient. The Bayley's scales of infant development were administered before, after 1 week, and after 3 months of iron treatment with appropriate placebo controls. These infants were tested further after 6 months with unchanged results [4].

Results of psychomotor studies in infancy

Four major questions related to iron deficiency were answered with these studies and are discussed below.

At what stage of iron deficiency is infant behavior adversely affected?

It was clear in both studies that a decrease in hemoglobin below the conventional cutoff limit for anemia was necessary to significantly affect mental and psychomotor development scores. This has also been the case for most similar studies. The performance of the iron-deficient infants without anemia as a whole was indistinguishable from that of the iron-replete controls.

In the Chilean study [2] among anemic infants, hemoglobin (Hb) concentration was correlated with performance. The lower the Hb, the lower the developmental scores. Similarly, in the Costa Rican study, infants with moderate iron deficiency anemia (Hb < 100 g/L) had lower mental and motor test scores than appropriate controls. The Santiago study [2] also evaluated the effect of chronic anemia. Infants whose anemia had duration of 3 or more months had significantly lower mental and motor development indices than did those with anemia of shorter duration. The results of other research published to date support the conclusion of these two studies: iron deficiency severe and chronic enough to cause anemia is associated with impaired achievement in developmental tests in infancy, and as anemia becomes more severe [5], deficits are more profound [5–8].

Why is severe iron deficiency—enough to lead to anemia—necessary to affect behavior?

This is an unanswered question. Animal experimentation shows that brain iron is acquired early in postnatal life; has a very slow turnover and when an iron deficient diet is provided, the decrease in hemoglobin production coincides with the depletion of tissues [9–11]. Therefore, anemia may be a reflection of tissue iron depletion severe enough to somehow affect behavior. On the other hand, the behavior measures available for this age group might be insensitive to subtle changes that may be present before the progression to anemia.

Effect of iron treatment

Consistent results have been obtained in studies that have included a placebo treatment group. Together, these studies indicate that short-term increases in test scores observed among iron-treated anemic infants are not significantly greater than those among placebo-treated anemic infants, but are thus likely related to a practice effect.

Although separating the effects of iron deficiency without anemia from those of IDA is important, a more pertinent question from a clinical perspective is whether iron therapy completely corrects behavioral abnormalities regardless of how soon the changes are detectable. Studies in Costa Rica [1], Chile [2], the United Kingdom [12], and Indonesia [6] included an iron treatment period of 2 to 4 months after which psychomotor development tests were repeated. Despite improved iron status, most of the formerly anemic infants were unable to improve their psychomotor performances. The only study to date that showed a convincing reversal of lower BSID scores is the Indonesian study [6].

Notwithstanding, in most of the studies iron therapy, even complete iron repletion was ineffective in improving the psychomotor scores of anemic infants to the level of nonanemic controls. The protocol in Indonesia [6] shows that studies in this field may give conflicting results and that newer and more imaginative techniques must be used to elucidate current controversies.

Specific patterns of failure

The Chilean study [2] found that with regard to the mental scale, fewer anemic infants than control infants successfully completed tasks that required comprehension of language without visual demonstration. In the psychomotor scale balance in the standing position (sits from standing, stands alone, and stands up) and walking were accomplished by significantly fewer anemic infants than controls (see tables 1 and 2). Similar findings were reported in the Costa Rican study [1].

Information about other behavioral differences has been limited. Previous work relied primarily on rating scales during developmental testing, and most studies used the Bayley Scale's Infant Behavior

TABLE 1. Mental scale items (12 months)

| Description (item no.) | Infants passing (%) | | p value |
	Anemic	Control	
Pushes car along (99)	56	77	NS
Turns book pages (103)	69	83	NS
Imitates words (mama, dada) (106)			
At 12 months	13	47	0.01
At 15 months	75	100	0.07
Says two words with meaning (113)			
At 12 months	0	7	NS
At 15 months	42	93	0.005
Points own toys, shoes or clothing (117)			
At 12 months	0	18	NS
At 15 months	25	60	0.07

TABLE 2. Motor scale items (12 months)

| Description (item no.) | Infants passing (%) | | p value |
	Anemic	Control	
Walks with help (42)	85	97	NS
Sits from standing (43)	67	97	0.01
Pat-a-cake (44)	82	97	NS
Stands alone (45)	64	93	0.02
Walks alone (46)	38	67	0.05
Stands up from sitting (47)			
At 12 months	3	7	NS
At 15 months	42	80	0.05
Stands on left foot with help (52)			
At 12 months	0	10	NS
At 15 months	8	40	0.05

Record. Nonetheless, observations have suggested a pattern of alterations. Infants with IDA were rated as unusually fearful, tense, restless, hesitant, withdrawn, or unhappy during testing [13]. In addition, infants with iron deficiency without anemia have been rated as more "solemn" than infants with better iron status. The only study to examine behavior in a context other than developmental testing of infants with documented IDA was conducted by Lozoff and colleagues in Guatemala [14]. During a short free-play period, quantitative coding of behavior showed that iron-deficient anemic infants and their mothers maintained closer proximity to each other than did comparison group dyads. The authors postulated that the pattern of closer proximity reflected heightened attachment behavior, a counterpart of the fearfulness and hesitance noted on behavioral ratings during developmental testing and evidence of altered affect, activity, or energy.

The preventive trial in Chile

The children in this protocol participated in two studies that comprised a recent project [15]—a preventive trial. Study I, a clinical trial of the developmental effects of preventing IDA, involved 1700 healthy Chilean infants and their parents living in suburban areas near the capital city of Santiago. The infants, who were 4 to 5 months old and receiving well-child care in the designated community clinics, were screened for the following entrance criteria: residence in the targeted area, birth weight ≥ 3.0 kg, no major birth or neonatal complications, no jaundice requiring phototherapy, no hospitalization at any age, no iron-containing preparations at any age other than those given by the study, and no major acute or chronic illness.

Qualifying infants were randomly assigned to a high-iron or no-added-iron condition at 6 months of age. Infants who were already receiving more than 250 ml/day of unmodified cow's milk or formula were randomly assigned to iron-fortified formula or no-added-iron milk. Breast-fed babies consuming < 250 ml/day of cow's milk or formula were randomly assigned to receive vitamins with or without iron and once cow's milk was introduced, the formerly assigned type of milk. Prior to randomization, a venipuncture excluded the few who were anemic (Hb < 110 g/L plus two or more abnormal biochemical measures) from the preventive trial. Hematologic assessments at 12 months were performed on all participants. The main outcome variable to assess developmental status of all infants was the Bayley Scales of Infant Development at 12 months, in addition to a visual attention measure at 6 and 12 months, a temperament measure, and determination of the timing of motor milestones. Study II, consisting of neuromaturational evaluations, was done with the anemic infants at 6 or 12 months of age as below.

Because several studies have shown that the association between IDA in infancy and lower developmental test scores is confounded by environmental disadvantages, Study I of this project was a double-blind, placebo-controlled preventive trial in which healthy Chilean 6-month-old infants were randomly assigned to supplemental-iron or no-added-iron treatments until 12 months of age. At 12 months, the supplemented group had less anemia (Hb < 110 g/L) and less iron deficiency without anemia (two or three abnormal measures: free erythrocyte protoporphyrin (FEP), mean corpuscular volume (MCV), or serum ferritin (SF); however, in contrast to a recent smaller preventive trial in Canada [16], we could not show higher Bayley mental (MDI) or psychomotor (PDI) development index scores related to absence of anemia.

For Study I, healthy full-term Chilean infants who were free of iron-deficiency anemia at 6 months were
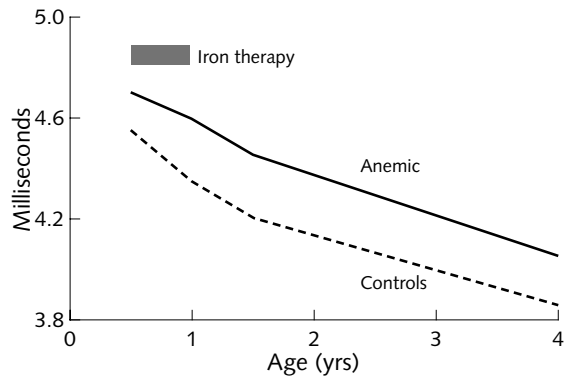
FIG. 1. Evoked auditory brain stem potentials (ABS) of the anemic and control children at 6 months and up to 4 years. The differences in speed of central conduction time in milliseconds are significant at all points ($p < 0.001$).

assigned to high- or low-iron groups or to high- or no-added-iron groups. Behavioral/developmental outcomes at 12 months of age included overall mental and motor test scores and specific measures of motor functioning, cognitive processing, and behavior. There were no differences between high- and low-iron groups in the prevalence of iron-deficiency anemia or behavioral/developmental outcome, and they were combined to form an iron-supplemented group ($n = 1123$) for comparison with the no-added-iron group ($n = 534$) At 12 months iron-deficiency anemia was present in 3.1% and 22.6% of the supplemented and unsupplemented groups, respectively. The groups differed in specific behavioral/developmental outcomes but not global test scores. Infants who did not receive supplemental iron processed information slower. They were less likely to show positive affect, interact socially, or check their caregivers' reactions. A smaller proportion of them resisted giving up toys and test materials, and more could not be soothed by words or objects when upset. They crawled somewhat later and were more likely to be tremulous. The results suggest that unsupplemented infants responded less positively to the physical and social environment. The observed differences appear congruent with current understanding of the effects of iron deficiency on the developing brain. The study shows that healthy full-term infants may receive developmental and behavioral benefits from iron supplementation in the first year of life.

Long term effects of iron-deficiency anemia on cognitive performance

The long-term effects of IDA have been addressed by two recently described follow-up studies in 5-year-old Costa Rican [17] and Chilean [18–20] children who had been well characterized as infants in both iron status environmental variables and psychomotor

development. These children were the subjects of respective reports during their infancy described above [1, 2]. At 5 years of age, an evaluation with a comprehensive set of psychometric tests showed that those who as infants had presented with IDA had lower scores on many of these tests when compared with children with higher hemoglobin in infancy. These disadvantages persisted after statistical control of many potentially confounding variables. At this age (5 years), measures of cognitive development are better predictors of future achievement, so they are even more reason for concern. For example, a 5-point drop in intellectual quotient (IQ) was consistent in both studies, as well as in other tests concerned with intellectual function. Five points of IQ are a significant handicap affecting millions of infants that have or have had anemia worldwide. This is worrisome because this is a preventable deficit.

Neuromaturation studies

IDA has long been thought to have central nervous system effects. However, finding direct evidence of such impact in the human infant has presented many methodological challenges. Auditory brainstem responses (ABR), which represent the progressive activation of the auditory pathway from acoustic nerve (wave I) to the lateral lemniscus in the brain stem (wave V), provide a non-invasive means of examining an aspect of the central nervous system that is rapidly maturing during the age period when iron deficiency is most common. Another rapidly maturing process in infancy is the balance of the autonomic nervous system. Experimental animals have also aided in orienting human studies.

Studies of ABR responses in infants with IDA

As part of Study II we studied auditory brain stem responses (ABR) during spontaneous naps in 55 healthy 6-month-old Chilean infants with IDA and 26 nonanemic controls [21, 22]. Central Conduction Time (CCT), the Wave I-IV interpeak latency, was longer in the iron-deficient anemic group, with differences becoming more pronounced at follow-up at 12 and 18 months, despite effective iron therapy, and continuing to be slower at a 4 years of age follow-up (fig. 1) [23–26]. The CCT is considered an index of central nervous system development, because myelination of nerve fibers and maturation of synaptic relays lead to an exponential reduction in CCT from birth reaching adult levels at 24 months. The pattern of resulting differences in latencies but not amplitudes, in longer CCT (as an overall measure of nerve conduction velocity) indicates that altered myelination is an appealing explanation, especially in view of recent laboratory work documenting iron's essential role in myelin formation and maintenance [27–31]. This study shows that IDA adversely affects at least one aspect of

central nervous system development in 6-month-old infants that lasts at least to 4 years of age and suggests the benefits of studying other processes that are rapidly myelinating during the first 2 years of life.

Sleep studies and autonomic nervous system development

Maturational patterns of heart rate variability (HRV) provide noninvasive tools for the investigation of central nervous integrity during early human development and are likely to reflect brain function alterations earlier and more closely than tests of behavior and psychomotor development. Patterns of heart rate and HRV were measured in 18 anemic 6-month-old infants and corresponding control infants from polygraphic recordings during quiet and active sleep and wakefulness [32, 33]. Iron-deficient anemic infants presented lower amplitude in all sleep-wake states. It was proposed that delayed myelination of the vagal nerve results in decreased parasympathetic influences that may underlie behavioral effects in iron deficiency in infancy.

Reliance on animal studies

The many challenges of studying the central nervous system in human infants has meant that direct evidence of central nervous system effects has had to come from animal studies. That evidence is increasingly compelling. In addition to earlier research on iron's role in central nervous system neurotransmitter function [34–38], recent work shows that brain iron is essential for normal myelination [27–31, 39, 40]. In rats, there is an influx of transferrin and iron into the brain in the immediate postnatal period. As iron and its transport and storage compounds are redistributed in the brain, myelinogenesis and iron uptake are at their peak. Iron and its related proteins concentrate in oligodendrocytes and become more concentrated in white than in gray matter (the majority of brain iron is found in this myelin fraction). Oligodendrocytes synthesize fatty acids and cholesterol for myelin production, a process that requires iron. Furthermore, animal studies have consistently found a lasting deficit in brain iron when IDA occurs early in development [9–11]. Although only two studies of iron deficiency in animal models examined myelination directly, both found iron-deficient rats to be hypomyelinated [29, 40].

Challenges in designing clinical studies

The results of these and other animal studies indicate that IDA during brain growth has long-lasting effects on the central nervous system. Yet obtaining evidence of similar effects in the human infant has posed many methodologic challenges. During the last 20 years, research on the effects of IDA and iron therapy on infant development has depended heavily on standardized tests of infant development, which have serious limitations and bear unknown relations to central nervous system functions. By measuring auditory-evoked potentials, we provide more direct evidence of central nervous system alterations in infants with IDA. Such neurophysiologic measurements had not been previously conducted in the iron-deficient infant.

Changes in auditory brainstem-evoked potentials or responses (ABRS) are particularly relevant to study in infants with IDA. ABRS consist of a succession of five to seven waves recorded at the scalp within the first 10 milliseconds after stimulation. Development changes in ABRS have been carefully studied. There are well-established developmental progressions from birth until stable values are reached at 18 to 24 months, with decreases in the absolute and interpeak latencies, decrease in duration, and increase in amplitude [21–23]. Latency changes have been related to increases in conduction velocity during axonal myelination. Other changes, such as increase in amplitude and reduction in duration, are probably due to improvements in synchronization at the axonal or synaptic levels. Thus, these developmental progressions are occurring during the age period when iron deficiency is most common.

Conclusions

Behavioral studies have consistently shown that IDA has adverse effects. Perhaps the most important implication of our findings, however, is that they may further generate plausible and testable hypotheses about the effects of iron deficiency on the developing central nervous system. Many parts of the brain are becoming myelinated in the first 2 years of life, when iron deficiency is most prevalent. We are obtaining more direct and indirect non-invasive measures of myelination in the human. With the hypothesis of impaired myelination in early IDA, it should be possible to design studies with specific measures, using techniques such as positron emission tomography (PET) scan imaging, evoked and spontaneous potentials, and, eventually, behavioral progressions known to depend on myelination. Such hypothesis-driven research would be a substantial advance over previous studies of iron-deficient infants, which has largely depended on global tests of development. Thus, these studies suggest new, promising directions for understanding more specific central nervous system mechanisms by which IDA could alter infant behavior and development.

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