Early and Long-term Effect of Iron Deficiency Anemia on Child Development

Tomas Walter

INTA, Universidad de Chile, Casilla, Santiago, Chile

Iron deficiency anemia, the most common single nutrient deficiency disorder in the world, has a peak prevalence among infants, affecting an estimated 25% of all babies (1). Because anemia is a late manifestation of iron deficiency, an even greater percentage of individuals of all ages show the biochemical changes of iron deficiency that precede the development of anemia.

Until recently it was often presumed that iron deficiency anemia had few deleterious effects unless severe enough to compromise cardiovascular function. However, it is now indisputable that iron deficiency can no longer be considered as a simple anemia easily reversible with iron therapy. It should be taken as a systemic disease, affecting many organs and systems (2). One of the most potentially devastating adverse consequences is that related to behavior and cognition. Evidence that iron deficiency has important behavioral effects has steadily accumulated during the past decade.

In human populations, nutritional disorders are not uniformly distributed—they are more likely to occur in the context of poverty, environmental deprivation, and disadvantaged social conditions, all of which may adversely affect behavior and development. Recent studies of the behavioral effects of iron deficiency have addressed these methodological challenges by increasingly careful attention to the social environmental and other factors that may be associated with iron deficiency.

STUDIES IN INFANCY

Because iron deficiency is most prevalent in the age range 6–24 months, which coincides with the latter part of the brain growth spurt and with the evolution of fundamental mental and motor processes, there have been more than a dozen studies during the past decade addressing the cognitive effects of iron deficiency during infancy, heralded by the pioneering work of Drs. Oski and Honig (3).

The two most recent studies—one performed in Costa Rica by Dr. Betsy Lozoff et al. (4), and the other performed by Dr. Tomas Walter et al. (5) in Santiago de Chile—are perhaps the least contaminated with the uncertainties that have prevented
any firm conclusions arising from the previous work. The noteworthy similarities in
the results of both protocols gives great solidity to their conclusions. It is remarkable
that these similarities were possible despite the fact that there are important differ-
ences in the study design, and that the research was carried out by two independent
investigators in two distant regions.

Walter's study was performed in association with a field trial of fortified infant
foods. Infants from a community clinic in the city of Santiago were included into a
food fortification study at 3 months of age and followed to 12 months of age. Complete
anthropometric, nutritional, morbidity, and socioeconomic data were collected. The
random fortification assignment ultimately turned out to be the strongest determinant
of the infant's iron status; all other intervening factors were essentially offset with
this design.

At 9 and 12 months of age, venipunctures for a full hematologic assessment were
performed. At 12 months, 7–10 days after the clinic visit, the first Bayley Scale for
Infant Development (BSID) was applied. After the first BSID, iron sulfate or placebo
was given for 10 days, at the end of which the BSID was repeated, and all infants
were given iron sulfate drops for three additional months and evaluated with a third
iron status assessment and BSID.

The BSID is a well-known and accepted tool for measuring psychomotor develop-
ment from 3–30 months of age and consists of a mental scale evaluating functions
related to the basic foundations of cognition, such as language acquisition and ab-
stract thinking. The motor or psychomotor scale relates to gross motor abilities such
as coordination, body balance, and walking. Both are age-adjusted to give an index
of mental and psychomotor development (MDI and PDI, respectively) very much
like an IQ, with a mean of 100 and an SD of 16 (6).

Protocols were designed to answer the following queries:

- How severe must iron deficiency be to affect behavior?
- The effect of duration of iron deficiency.
- The effect of short-term iron therapy (before correction of anemia).
- The reversibility of the changes after a long-term trial (enough to revert anemia).
- The specific areas of mental or motor processes most affected.

Degree of Iron Deficiency Affecting Behavior

The first question was studied because iron deficiency occurs along a physiologic
continuum. Reduction in total body iron occurs in three stages of progressively in-
creasing severity, based on current understanding of iron metabolism and defined
by appropriate laboratory criteria (7), as has been presented by other speakers in
this workshop. At what point in the continuum of iron deficiency is infant behavior
adversely affected?

In the study by Walter et al. (5), the criteria for classification into three groups
[anemic, control, and nonanemic iron-deficient (NAID)] was retrospective (Table 1).
The broad heterogeneity of the NAID prompted its reclassification into grades of severity. It is noteworthy that these controls comply with the most rigorous possible criteria for defining iron repletion and that the subclassification of NAID succeeded in discriminating degrees of severity.

It becomes clear in this study that a decrease in hemoglobin leading to overt anemia was necessary to affect mental and psychomotor development scores (Fig. 1). The performance of the NAID infants as a whole was indistinguishable from that of controls. In none of the NAID subclassifications could differences be shown.

The recent study by Lozoff et al. (4) addressed this issue by enrolling in a single study a relatively large number of otherwise healthy infants with varied iron status. These children were recruited in a cross-sectional survey as opposed to the longitudinal follow up of Walter's infants. The infants were divided into groups ranging from most to least iron-deficient. The data on the anemic infants were further analyzed with respect to severity of anemia (moderate or mild). The BSIDs were administered before and after 1 week and after 3 months of intramuscular or oral iron with appropriate placebo controls.

Infants with moderate iron deficiency anemia (hemoglobin <100 g/l) were found to have lower mental and motor test scores than those of appropriate controls, and infants with mild anemia (hemoglobin 101–105 g/l) had lower motor scores but not lower mental scores. The mean mental test score of the moderately anemic infants was eight points below that of infants with higher hemoglobin levels, and the mean motor score of the entire anemic group was 10 points below that of infants with hemoglobin >105 g/l. Infants with iron depletion or iron deficiency with intermediate or normal hemoglobin levels did not have lower mental or motor developmental test scores.

The results of research published to date support the conclusions of the studies in Chile and Costa Rica, that iron deficiency severe enough to cause anemia is associated with impaired performance on developmental tests in infancy. In sum, all five published studies with careful definition of iron status and nonanemic control...
groups, conducted in Guatemala, Chile, the United Kingdom, and Costa Rica, found clinically and statistically significantly lower mental test scores among anemic infants prior to treatment. Lower motor test scores among anemic infants were also noted in four of the five studies.

Effect of Hemoglobin on Development Scores

Examining mental and psychomotor developmental indices based only on hemoglobin, as the most common indicator of iron status, Walter et al. (5) defined a sigmoid distribution with hemoglobin intervals of 5 g/l (Fig. 2). Thus, among anemic infants, hemoglobin concentration was correlated with performance, so that infants with moderate anemia (hemoglobin 84–104 g/l) had significantly lower scores than those with mild degrees of anemia (hemoglobin 105–109 g/l). These, in turn, had poorer indices than infants with hemoglobin >110 g/l with no graded improvements seen at higher hemoglobin level.
Effect of Duration of Anemia

Walter et al. (5) were able to evaluate the effect of chronicity due to the unique longitudinal characteristic of the protocol. To do this, they studied the effect of iron status at 9 months of age on development indices measured at 12 months. Infants who were anemic both at 9 months and 12 months, whose anemia had a duration of 3 or more months, were compared with those anemic at 12 months but not at 9 months—that is, those whose anemia were presumed to be present for less than 3 months. Those infants anemic for more than 3 months had significantly lower mental and motor development indices than those anemic less than 3 months. It is reasonable to assume that if nonanemic infants with marginal iron status at 9 months were to continue with an iron-deficient diet, their anemia would increase in duration (and severity) and their psychomotor performance would hence deteriorate further. These
two characteristics of anemia—duration and severity—could not be completely individualized with the current design.

**Effect of Iron Therapy**

**Rapid Changes with Iron Treatment**

Consistent results have been obtained in all four studies that included a placebo treatment—the investigations by Lozoff in Guatemala and Costa Rica, Oski and Honig's original study, and the second study of Walter et al. 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; increases in scores were observed regardless of the treatment the infants received or their iron status prior to treatment. The results of these studies confirm that an increase in Bayley test scores can be expected if the Bayley Scales are readministered after a short time period and that these improvements probably indicate the effect of practice because they cannot be attributed to iron therapy.

**Complete Correction with Iron Therapy**

Although separating the effects of iron deficiency from those of anemia is important, a more pertinent question from a clinical perspective is whether or not iron therapy eventually completely corrects any behavioral abnormalities, regardless of how soon changes might be detectable.

Lozoff's recent study in Costa Rica was specifically designed to examine the effects of a course of treatment commonly used in practice—3 months of oral iron therapy. Anemia was corrected in all infants, but, as would be expected, some of them still showed biochemical evidence of iron deficiency, in particular high FEP or low ferritin levels. On the basis of hematologic response to iron therapy, infants who became repleted with iron by the end of the study were distinguished from those in whom all evidence of iron deficiency was not corrected. Most of the group that was initially moderately anemic did not become completely iron-replete after 3 months and concluded the study with mental scores that were still significantly lower than those of infants with initial hemoglobin levels >100 g/l, regardless of whether the latter were iron-repleted after 3 months or not. Three months of iron therapy was sufficient to correct iron deficiency completely in only nine moderately anemic infants (26%). Lower mental test scores were no longer evident among these infants. However, the absence of a post-treatment difference was due not to significant improvements in the mental test scores of the formerly moderately anemic infants but to the slight but statistically significant decline in mental scores after 3 months in the comparison group. In contrast to the pattern of mental test score results, the 18 previously mildly or moderately anemic infants who became iron-replete by the end of the study did show a substantial increase in motor test scores, averaging 10 points,
while the motor scores of infants with hemoglobin levels >105 g/l who became iron-replete remained approximately the same. Previously mildly or moderately anemic infants who did not become iron-replete concluded the study with motor scores that were still substantially lower than those of infants with initial hemoglobin levels >105 g/l. There was laboratory evidence that anemic infants who did not become iron-replete after 3 months had more severe and more chronic iron deficiency.

Lack of improvement after iron therapy has also been the primary finding in two other studies, one in the United Kingdom and the other in Chile. Aukett et al. (8), in a double-blind randomized study of 17- to 19-month-old iron-deficient children in the United Kingdom, found that even among those who showed a distinct hematologic response to 2 months of therapeutic iron (hemoglobin increase >20 g/l), most (58%) failed to show the rate of development expected for their age. This study, in conjunction with the one in Costa Rica, suggests that iron therapy may favorably affect developmental test scores among some anemic infants, but not the majority. The only other study relevant to the question of longer-term iron therapy is the second study by Walter et al. (9) in Chile, which is directly comparable in design to that in Costa Rica. As in the latter study, the administration of oral iron was carefully supervised and an excellent hematologic response documented. However, in contrast are the results obtained in Costa Rica and the United Kingdom, even those anemic infants in whom hematologic status was corrected failed to improve their scores. Thus no improvements in mental or motor test scores were observed after 3 months of treatment, even though anemia was reversed in all infants and hematologic measures of iron status were completely corrected in 11 of the 39 formerly anemic infants.

Specific Patterns of Failure

Walter's protocol examined the specific test items involved in the raw score that, when normalized for age, yield the development index. Because all infants were the same age, raw items were also the same.

With regard to the mental scale (Table 2), items that require comprehension of language but do not involve a visual demonstration were passed by significantly fewer anemic infants than controls.

In the psychomotor items, those items relating to balance in the standing position and walking (sits from standing, stands alone, and stands up) were passed by significantly fewer anemic children than controls (data not shown).

Because the follow-up period in the Costa Rican, Chilean, and British studies was only 2 or 3 months, these studies cannot determine whether ill effects of iron deficiency anemia persist beyond infancy. This has been investigated in the long-term follow up of these infants.

EFFECT OF ANEMIA AT 12 MONTHS ON COGNITION AT 5 YEARS

The infants from the studies of Walter in Chile and Lozoff in Costa Rica were followed to 5 or 6 years of age. These infants thus had a very detailed history of
TABLE 2. Mental scale items at 12 and 15 months (percentage of infants passing)*

<table>
<thead>
<tr>
<th>Description (item no.)</th>
<th>Infants passing (%)</th>
<th>p valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anemic</td>
<td>Control</td>
</tr>
<tr>
<td>Pushes car along (99)</td>
<td>56</td>
<td>77</td>
</tr>
<tr>
<td>Jabbers expressively (101)</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Uncovers blue box (102)</td>
<td>31</td>
<td>47</td>
</tr>
<tr>
<td>Turns book pages (103)</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>Pats whistle-doll (in imitation) (104)</td>
<td>44</td>
<td>63</td>
</tr>
<tr>
<td>Imitates words (mama, dada) (106)</td>
<td>13</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>At 12 months</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>At 15 months</td>
<td>42</td>
</tr>
<tr>
<td>Says two words with meaning (113)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>At 12 months</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>At 15 months</td>
<td>25</td>
</tr>
<tr>
<td>Shows own shoes, toy, clothing (117)</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>At 12 months</td>
<td>25</td>
</tr>
</tbody>
</table>

* From ref. 5.

b Analyzed by $\chi^2$ of absolute numbers.

c NS, not significant.

iron status, growth and development, socioeconomic events, and other possible variables that might influence behavior. Moreover, these infants were treated with sufficient iron to complete the correction of their iron status in infancy, so any effect of chronic lack of iron was discounted.

At 5 years of age the repertoire of psychological tests than can be applied is much larger, and has greater significance with respect to future achievement, than the BSID, as has been stated.

In the study by Walter et al. (9), the two groups at the extremes of iron status were tested: the formerly anemic ($n = 43$) and the former iron-replete controls ($n = 29$). The battery of tests used encompassed a general intelligence test (the Stanford–Binet Scale), a test of fine and gross motor performance (the Bruininks–Oseretsky test of motor proficiency), a sophisticated test of psycholinguistic capabilities (Illinois), a test of visual–motor integration (Beery), and an educational school preparation scale (Woodcock Johnson preschool scale).

All the children were tested at 66 ± 5 months except for the Illinois language test, which was applied at a mean of 72 months.

The formerly anemic children, now at 5 ½ to 6 years of age and having been treated appropriately according to current medical practice, showed the persistence of lower performances when compared to their formerly iron-replete peers (Fig. 3) (9).

Lozoff et al. (10) were able to study all the children formerly nonanemic ($n = 126$) and compared them with the moderately anemic infants ($n = 28$), looking for subtle changes in the nonanemic-iron-deficient group. The findings are entirely comparable to Walter’s study in that the formerly anemic children performed slightly but significantly worse than their nonanemic peers.
FIG. 3. Cognitive tests of 5½-year-old children who were anemic at 12 months of age. Formerly anemic infants perform poorly when compared with formerly iron-replete controls.
These findings are extremely worrisome. They suggest the long-term persistence of a cognitive deficit in children who presented with anemia during infancy and who were treated according to commonly accepted good medical practice. Moreover, the tests now used are extremely good predictors of future achievement, and even though the differences may seem small in absolute values for each individual child, they acquire intimidating magnitude when extrapolated to a global scale. It must be kept in mind that even industrialized societies are not exempt of iron deficiency during infancy. The United States has documented a prevalence of close to 10% as a whole, and in the lower income bracket the figure is 23% (11).

REFERENCES


DISCUSSION

Dr. Viteri: This work is extremely important and I congratulate Tomas Walter and the Chilean group for conducting studies of this type. Given the information presented, the effect of early iron deficiency may have its basis in biochemical alterations in the brain, as has been shown in experimental animals. How permanent are the effects I wonder? You seem to be indicating that anemia may affect mental performance in the long term. This contrasts with the work of Pollitt et al. (1,2), who showed that treatment of anemic children at preschool and school age appeared to result in improvement in performance. My question is, How firm is the hypothesis that if you miss a developmental stage it can never be recovered? My second question is, Why has only anemia, and not iron deficiency without anemia (or other factors), been shown to be deleterious? Thirdly, your data seem to show that neurologic immaturity, which is very intimately correlated with iron deficiency, is a critical factor, and here I should
like to know how much of an interaction exists between factors that are associated with neurologic immaturity and those that are associated with iron deficiency anemia. How can you attempt to separate these interactions? In other words, how would you go about establishing a causative relation rather than a confounding association?

Dr. Walter: The issue of the "window of vulnerability" is a big one. In the Pollitt studies, iron treatment reversed the impairment in performance in preschool and school age children. In ours, it did not. I think it is conceivable that there is indeed a window of vulnerability in early infancy somewhere, and this question needs to be addressed. The discrepancy between the studies has not been resolved. Why iron deficiency anemia and not iron deficiency without anemia affects development I have no idea at all.

As far as confounding effects are concerned, it seems to me that the only way to avoid such effects would be to treat infants very early with adequate iron supplements. This would exclude an effect of iron deficiency from among other influences on development.

Dr. Brabin: My question relates to the design of this very important study. Am I correct that in anemic cohort there was a significantly greater proportion of girls, and if that is correct are there any sex differences in developmental scores that need to be taken into account?

My second point relates to the mothers' education. This seems to have been better in the anemic group. Though you controlled for this in your statistical analysis, it does raise the question as to whether the more educated mothers were more likely to be in employment and hence away from home at a time when their children might suffer from the lack of stimulation this entails.

In relation to the language delay that you demonstrated, you mentioned that iron has an important location in the auditory pathway. Could it be that there are differences in hearing between the groups which might explain some of the language impairment?

Finally, I should like to highlight the studies of Agarwal, who has been investigating iron deficiency and mental development over many years. He is of the view that iron deficiency early in pregnancy has an important effect on brain growth and that this cannot be reversed even with correction of iron deficiency anemia late in pregnancy. In support of this, he has carried out confirmatory investigations in rats. He has also shown that the function of several placental enzymes is impaired in mothers who have iron deficiency in early pregnancy.

Dr. Walter: I think that the difference in results according to sex was due to the fact that I was only presenting the extremes. With respect to employment, I can confirm that all mothers were at home looking after their children before they were 1 year of age since this was an important prerequisite for obtaining reliable nutritional data. There was no difference in employment rates between the groups at 5 years of age.

In current collaborative studies we are looking at neurological maturation, and particularly at visual function, brain stem auditory evoked potentials, and integrative nervous system functions such as sleep. Auditory evoked potentials will be compared in iron-deficient and normal infants.

Dr. Gibson: Children who are iron-deficient often have diets that are low in animal products and high in plant-based foods. Such diets are also low in available zinc, so that children consuming such diets may be at risk of zinc deficiency. There is animal and human work that suggests that zinc has a role in brain function. I wonder whether you had an opportunity to examine zinc status in the children in your study.

Dr. Walter: In the first study we measured plasma zinc and found very low values in all infants, with no differences between the groups. About 60% of the infants had plasma zinc concentrations below 60 μg/dl. We are planning a zinc supplementation study, but in a different setting, looking more at growth velocity than cognitive performance.
Dr. Gibson: It seems to me that it would be of interest to include infants given zinc supplements alone and infants given iron + zinc supplements.

Dr. Zipursky: Could you clarify the randomization process used in your study? Is there an explanation for the unequal distribution of maternal characteristics? Also was there a difference in developmental status in the supplemented group overall, compared to the control group?

Dr. Walter: The studies were not planned as psychological studies, but as iron nutrition intervention studies. We did not randomize environmental characteristics when we compared anemic versus nonanemic infants. This is a sensitive point and our current design for a larger study takes these factors into account.

Dr. Zipursky: I am not clear how the groups were randomized. Did one receive supplement and the other not?

Dr. Walter: They were randomized at 4 months of age as to whether they received iron-fortified or nonfortified milk. Being for several months on a fortified formula of course made the infants less likely to be anemic. At the end of the study we had separation into anemic and nonanemic groups, but naturally some anemic children came from the fortified group and some nonanemic children came from the nonfortified group. So the randomization at the end was not based on what group they belonged to initially but whether they were anemic or not.

Dr. Cook: I am interested that your observations were limited to anemic children. Is it possible that your findings are the result of anemia from any cause, not only from iron deficiency? Maybe a second study should be done in which another group of infants with anemia, perhaps the result of a self-limiting infection, is compared with a group with iron deficiency anemia for later deficits in cognitive performance.

Dr. Walter: We would have liked to have had an anemic control group, but anemia in Chile is virtually always due to iron deficiency. Infection would be likely to influence the results of developmental testing independently of any anemia it might cause, so I don’t think it would be a good model. The closest we have attempted to dissociate anemia from iron deficiency is to give a short course of iron therapy sufficient for iron to become available but not enough to correct the anemia. We have not found any differences in psychomotor performance in such short-term trials, nor has anyone else.

Dr. Bell: Perhaps I missed this, but did diet have any influence on the developmental outcome?

Dr. Walter: We could not find any influence of different dietary factors on outcome except for breast-feeding. Infants breast-fed exclusively for 7 months or more had better scores than did the remainder who were breast-fed for less than 7 months. So breast-feeding at 1 year of age is very important. Dietary iron was not found to be a significant factor in outcome, even though the intakes were very carefully recorded.

REFERENCES