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Psychomotor Development and Behavior in Iron-deficient Anemic Infants

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Research has shown an association between iron deficiency anemia and adverse effects on behavior and psychomotor development in infants and children. The exact mechanisms behind these associations are not fully understood. Additional research is necessary.

Introduction

The scientific community showed great interest in the effects of infant malnutrition on cognitive development during the 1960s and 1970s. Work published by Oski and Honig in 1978[1] broadened this interest to include the effects of iron deficiency. Their work was the starting point for several studies that investigated the impact of iron deficiency anemia on infant development. The results are inconclusive, despite various studies that attempted to improve on the initial methodologic limitations.

Several factors illustrate the importance of continued research into the effects of anemia on infant development. First, the greatest prevalence of iron deficiency anemia occurs between 6 and 24 months of age. During this period, rapid brain growth occurs and cognitive and motor skills are developed. Second, the presence of high concentrations of iron in some areas of the brain (substantia nigra, globus pallidus, nucleus caudate, red nucleus, and putamen) and the incorporation of iron in brain tissue during rapid growth of the nervous system indicate the probable participation of iron in the neurophysiologic processes of behavioral organization. Third is the difficulty observed in recovering brain iron levels in experimental animals made iron deficient during early periods in their development, even though they were treated with iron.[2–5]

Extensive and detailed reports[6–8] concerning the relation between infant iron deficiency and behavior exist. This analysis focuses on the most recent publications and on the preliminary results of a collaborative study being conducted by the University of Michigan and INTA, University of Chile, Santiago, Chile.

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Methodology

Almost all studies of the relationship between iron deficiency anemia and behavior have been based on psychomotor development scales, which have significant shortcomings. A major limitation of these development scales is that they were developed according to normal tendencies, i.e., they are related to the normal time of accomplishment of mental, social, language, and other skills among infants of a given age. They do not, however, evaluate the efficacy in the use of mental process, nor do they provide a basis to judge the relevance of a minor delay from a developmental perspective. The scales offer a low level of prediction of future accomplishments for infants who exhibit achievements within the normal range. Additionally, the application of the scales continues to be highly dependent on the evaluator, even though an instruction manual with an operational description for each item is available for the most developed tools. The scales continue to be, however, the most commonly used method for evaluating infant development despite these and other limitations.[9,10]

The majority of the most recent studies of anemia and behavior make use of the Bayley[11] development scale, which includes an estimate of a Mental Development Index (MDI) and a Motor Development Index (PDI). The Bayley scale also makes available a Behavior Record Scale. However, the fact that infants have been studied at different ages and with different levels of anemia has made the comparison of results obtained for both development and behavioral scales difficult.

Another problem encountered during the methodologic analysis of the studies is the different criteria used in the definition of an iron nutrition state. Fortunately, this difficulty has been overcome, and the latest research includes a hematologic diagnosis based on at least three hematologic measurements, hemoglobin, and hematocrit (transferrin saturation, mean corpuscular volume, erythrocyte protoporphyrin, and serum ferritin). Some studies also include the hematologic response to iron treatment (with adequate compliance), which is undoubtedly the best method of confirming the initial diagnosis.[7]

As observed in malnutrition, iron deficiency can coexist with other nutrition deficiencies. For that reason, conclusive findings are more difficult to attain. Iron, lead, and zinc are micronutrients closely related to diet. Strong evidence has been found to associate lead exposure with cognitive development, although a causal relationship has not been established. Infants exposed to high lead levels during the prenatal stage and the first years of infancy show significant decreases in developmental outcomes and subsequent deficiencies in cognitive, motor, and mental achievement tests.[12,13] Recently, interest in the study of zinc deficiency and cognitive development has arisen. Experimental evidence with animals and clinical descriptions of infants emphasize behavioral changes associated with zinc deficiency.[14]

Iron deficiency anemia is most prevalent among low-income populations, but also affects infants from different socioeconomic levels. Other risk factors related to infant psychological development include premature birth, low birth weight, malnutrition, adolescent parents, single mothers, missing fathers, maternal depression, low parental education level, and parental psychiatric problems.[15–22] These risk factors generally do not occur independently of one another; the presence of one does not simply add to the presence of another but is synergistic. As a result, the combination of a greater number of risk factors among the underprivileged increases the risk for impaired infant cognitive development.[23,24]

More recently, resilience to potential risk factors has been highlighted. Adequate prenatal care, improved birth weight, better upbringing, safe and stable mother-infant relationships, presence of the father, and varied home stimulation are some protective factors that can diminish the potentially adverse effects for infant development.[10]

A further and confusing factor in the study of the relationship between iron deficiency anemia and behavior is the presence of socioenvironmental conditions, which may confuse, lessen, or amplify the situation to be observed. It is fundamental to include in future studies an analysis of contextual variables, including biologic and psychosocial background information on infants who have iron deficiency anemia.

Iron Deficiency Anemia and Infant Psychomotor Development

Case-Control Studies

Studies by Lozoff et al.[25] in Costa Rica and by Walter et al.[26] in Chile provide data that allow an analysis of the relationship between iron deficiency and psychomotor outcomes during infancy. Both studies were carried out in infants of low socioeconomic levels in developing countries.

The Chilean study was started in 1983 and formed part of a field research study on infant food fortification. A cohort of healthy, full-term 3-month-old infants who attended a health clinic in Santiago were included in an iron supplementation study. They received monthly health care checkups and weekly home visits to the age of 12 months. Infants who were spontaneously weaned at 3 months randomly received either iron-fortified or nonfortified cow's milk that was routinely distributed in the health clinics. Infants who continued to be breastfed at 3 months were randomly assigned to fortified or nonfortified cereal. The sample was thus divided nonrandomly into two groups according to the length of breastfeeding and randomly within each group according to the fortification (or not) of milk or cereal. Anthropometric, dietary, morbidity, and social background information was collected. Hematologic venipuncture samples were made at 9 and 12 months to determine hemoglobin (Hgb), mean corpuscular volume (MCV), and free erythrocyte protoporphyrin (FEP) levels. The children were evaluated by the same psychologist with the complete Bayley scales 10 days after the second hematologic examination. The psychologist was blind, as was the mother, to the hematologic status of the infant tested.[26]

A complete hematologic evaluation was carried out in 196 12-month-old infants who were classified into three groups: the control group (n=39) having Hgb > 110 g/L and all other biochemical measures within normal values; an anemic group (n=39) having Hgb < 110 g/L and at least two altered biochemical measures; and a nonanemic iron-deficient group (n=127) having Hgb > 110 g/L and at least one altered biochemical measure. This hematologic classification was later corrected according to the response to iron therapy administered after the 12-month psychomotor assessment.

Anemic infants' development scores were lower than those of both control groups and the nonanemic iron-deficient group. Anemic infants' scores on the mental scale were within normal values, but six to seven points below the nonanemic iron-deficient group and the control group (96.4 ± 8.11, 103.4 ± 9.0, and 102.1 ± 9.8, respectively; $p < 0.0001$). Similarly, the anemic infants reached scores on the motor development scale nine to 11 points lower than the other groups (90.0 ± 12.5, 98.7 ± 11.3, 101.2 ± 11.5; $p < 0.0001$). No differences were observed between the control group and nonanemic iron-deficient group for either the MDI or PDI. The severity of the infants' anemia was related to lower psychomotor scores. Infants with Hgb < 100 g/L had lower MDI and PDI than did infants with milder levels of anemia (Hgb > 105 and < 109 g/L).

The 9-month hematologic evaluations illustrated the decline of psychomotor scores with prolonged anemia. Infants who were anemic at both 12 and 9 months (Hgb < 105 g/L) scored lower on the MDI than did infants who were anemic at 12 months but who showed Hgb > 105 g/L at 9 months (94.1 ± 4.1 versus 99.4 ± 10; $p < 0.05$). Similar results were found for PDI (86.0 ± 11.3 versus 93.7 ± 13.6; $p < 0.05$). Chronicity and severity are important factors to consider in any analysis of iron deficiency anemia and infant development, according to the data presented above. The infants in this study with longer-lasting anemia were probably the same as those who suffered a greater severity at 12 months, because the two factors are interdependent.[27]

The infants were randomly assigned to a short-term (10 days) oral iron or placebo treatment after their 12-month psychomotor development assessment. Improvements in the MDI and PDI scores for all groups under study were observed independent of iron and placebo treatment.

Oral iron treatment of 75 days (iron sulfate 3–5 mg/kg/day) did not produce improvements in verbal or motor scores at 15 months of age. All groups displayed small variations in the scores for MDI and PDI independent of iron status at 12 months. Only 13 of the 39 anemic infants achieved complete correction of their iron status. Analysis of this subgroup did not show improvement in development indices, because results continued to be inferior to those shown by both the control and the nonanemic iron-deficient groups.[27]

An analysis of the Bayley items was made to identify the specific skills where children more frequently failed. In the motor area, items related to balance and walking independently showed differences. Studies by Pollitt[28] suggest that a delay in the acquisition of motor skills, especially those associated with walking independently, is a factor common to nutrition deficiencies. That author has developed an explanatory hypothesis for the cognitive consequences of malnutrition that includes delays in reaching motor milestones. We refer to this hypothesis at greater length below. Iron-deficient anemic infants showed the greatest level of failure in the mental scale for items related to language. The Bayley Infant Behavioral Record (IBR), which corresponds to observations made during testing, suggested that anemic infants were less responsive to test situations, less attentive, and less active than were infants in the control group. When items related to the IBR were grouped according to the method proposed by Matheny,[29] anemic infants were observed to be less oriented to the task and to have an altered emotional state (frightened, tense, unhappy).

A multivariate analysis using the MDI and PDI as dependent variables was carried out. Independent variables included measures of social background and infant growth. Hemoglobin level was introduced as the first variable. It exercises a significant effect on the dependent variables and allows us to explain 4.3% MDI and PDI variability. A significant effect of height at 12 months of age was also observed.[27]

Results obtained in the study carried out in Chile should be interpreted cautiously, because the analyses do not differentiate between infants according to fortification (fortified or nonfortified). Thus, it is not possible to be certain whether infants who suffered anemia despite being part of a fortified group did so because they did not consume sufficient iron (ineffective supplementation) or because of other biologic or environmental factors. The results are, however, in agreement with those observed by Lozoff et al.[25] in an adequately randomized study in Costa Rica, and support is given to the conclusions of both studies.

The Costa Rica study[25] included 191 infants between 12 and 23 months of age in a randomized double-blind design. Psychomotor outcomes were compared in six groups of infants with differing iron states (34 moderately anemic, 18 mildly anemic, 45 with intermediate Hgb levels and iron deficiency, 21 with iron deficiency but without anemia, 38 nonanemic and iron depleted, and 35 iron sufficient). The study, begun in 1983, shows results similar to those of the study by Walter et al. described above.[26] Both mental and motor skills in psychomotor development are associated with Hgb level. The moderately anemic group (Hgb < 100 g/L) displayed normal outcomes, although they were inferior to those of infants with higher Hgb levels; the MDI was eight points lower and the PDI was 12 points lower. The mildly anemic group (Hgb 101–105 g/L) showed lower achievements in motor, but not in mental, scales. In a comparison of the anemic group as a whole (Hgb < 110 g/L) with the intermediate group (Hgb > 110), the PDI score was 10 points lower. Anemic infants continued to score lower on both scales even after 3 months of oral iron treatment.

However, anemic infants (Hgb < 105 g/L) whose iron deficiency was totally corrected by the end of the treatment showed an average improvement of 10 points in PDI, and thus achieved the same level as the nonanemic infants. Differences in mental scores also disappeared as the result of a decrease in the MDI scores for the nonanemic group. This decrease in the MDI scores for infants older than 18 months was described by Lozoff in a study in Central America.[7]

The results of the Costa Rican study described above[25] indicate, as does the study carried out in Chile, that the duration and severity of anemia are important variables that must be considered when evaluating the impact of anemia on development. The difference to be noted between the two studies is that Walter's research[26] shows diminishing MDI and PDI scores for both the moderately and the mildly anemic groups, whereas Lozoff's study[25] suggests that the impact varies depending on the skills being analyzed. Motor development is sensitive to mild levels of anemia, whereas mental skills show a decrease only with more severe, and probably more chronic, iron deficiency.

Another aspect of the Lozoff study is related to changes in behavior and mother-child interaction. According to the IBR, anemic infants were described as exhibiting greater behavioral alterations as much in emotional tone as in task orientation. Anemic infants were observed maintaining closer contact with their mothers, initiating interactions with them more frequently, and spending less time away from them during both mother-child play sessions and Bayley assessment coded in video. The mothers were less participative and encouraged their children less in the performance of tasks.[30,31] These observations raise questions of whether conditions before iron deficiency anemia could help explain differences in infant development.

A recent study carried out in Indonesia confirmed lower MDI and PDI scores in infants with iron deficiency anemia, but added information that offers different conclusions with respect to recovery from the observed effects. Idjradinata and Pollitt[32] conducted a randomized, double-blind study with infants 12 to 18 months old (50 iron deficient and anemic, 29 nonanemic and iron deficient, 47 iron sufficient). Within each group infants were randomly assigned to 4 months of iron or placebo treatment. Infants with Hgb between 105 and 120 g/L were excluded. Results showed that anemic infants reached MDI scores approximately 12 to 14 points below those of the other groups. Differences were not found between the iron-sufficient and the nonanemic, iron-deficient groups. Motor scores 14 to 17 points below those of the other groups were observed for the anemic group, and no differences were found between the two nonanemic groups. The anemic group, which received iron treatment, had a pronounced rise in both mental (+19 points) and motor (+23) scores. All of the groups showed a general improvement in their scores, but the iron-sufficient and the nonanemic, iron-deficient groups showed a less dramatic change (three to five points). The results of this study do not concur with those obtained by the earlier work of Lozoff et al.[25] and Walter et al.[26] with respect to reversibility of development score differences for anemic infants through long-term oral iron treatment. The Indonesian study was different in that a more prolonged (4 months) iron treatment was applied, but also in that long placebo treatment was given as well to an anemic group. Walter and Lozoff decided not to test this latter condition for ethical reasons. The infants in the Indonesian study came from better socioeconomic backgrounds, thus diminishing the participation of those covariables associated with the socioeconomic environment. Although this study had a rigorous design, further information is needed to give a definitive answer to the question of the reversibility of anemia's effects.

A different approach to the relationship between anemia and behavior is being taken in a study by the Neurophysiology Development Unit of INTA at the University of Chile. Peirano and colleagues are recording electrophysiologic signals during the sleep-wake cycle. Preliminary analysis suggests that the iron-deficient infants' maturation patterns are different from those of iron-sufficient infants. Anemic infants at 6 months show variations in the sleep-wake cycle, including a greater level of variability in respiration during sleep and marked motor activity during the initial periods of sleep, making stabilization more difficult. The study of motor activity with polygraphic records during the sleep-wake cycle shows that anemic infants have less mature motor activity patterns, suggesting that motor neurodevelopment is delayed. Anemic infants' heart activity patterns at 6 months are also immature. Variability of heart rate frequency is greater, which is not modified by prolonged (6 months) iron treatment.[33,34]

Registration of auditive-evoked potentials of the brain stem at 6 months shows that both absolute and interwave latencies in iron-deficient infants are longer than those for iron-sufficient infants. Similarly, central conduction time is longer. These observations suggest that the maturation of the central nervous system (CNS) in anemic infants is delayed. Nerve fiber and synaptic connection maturation during the first 2 years of life produces a progressive reduction of central conduction time. Anemic infants continue to show delay after receiving prolonged oral iron treatment (4 months of treatment of symptoms or 6 months of preventive treatment).

Roncagliolo et al. found that iron deficiency anemia adversely affected CNS development and suggested that myelination of the nervous tissue was the mechanism involved, owing to the central role played by iron in myelination.[35] The greater sensitivity of neurophysiologic methods with respect to psychomotor tests will make it possible to study the impact of iron deficiency on the integrity of the CNS, especially with respect to the important role of cerebral iron in myelination.

In summary, the studies described all show that iron deficiency anemia negatively impacts development. Adverse changes are not seen in nonanemic iron-deficient infants. The severity, duration, and time of onset of the deficiency are important factors to consider and should be studied further. The reversibility of the changes observed is an additional issue of great interest.

Preventive Studies

During the last 5 years, Lozoff and the Chilean researchers have conducted a field trial in an attempt to overcome the methodologic weaknesses of previous studies. Six-month-old infants received iron supplementation or placebo until they reached 12 months, according to a randomized prospective design. Infants were selected based on the following criteria: were full term with a birth weight > 3000 g, received no phototherapy treatment for neonatal jaundice, suffered from no chronic or acute illnesses, and attended one of four health clinics in the Santiago region. They were randomly assigned to receive either iron supplements or non-iron-supplemented formula (the latter corresponds to normal pediatric care in the clinic). Only infants with normal iron levels of Hgb (>105 g/L) at 6 months were included in the study; anemic infants received iron treatment and were part of a second protocol in the study. While taking part in the study, each infant received monthly health care checks and weekly home visits by project personnel to record growth and morbidity information. Family background variables were also registered (e.g., socioeconomic level, home stimulation, home stress level, and maternal intelligence). The infants were assessed at 12 months with the complete Bayley scale, followed by a second complete hematologic examination.

Preliminary results (n =944 [supplemented =625, not supplemented =319]) indicate that the groups were similar in their rates of growth, family variables, and hemoglobin levels when they entered the study. At 12 months, however, the supplemented group showed a lower level of anemia (Hgb < 110 g/L) and less iron deficiency (Hgb <110 and two of three abnormal biochemical parameters: MCV, FEP, or ferritin). Of the supplemented group, 4% had anemia and 15% had iron deficiency; of the nonsupplemented group, 24% had anemia and 49% had iron deficiency. No differences were found between the MDI and PDI indices for the two groups (supplemented MDI = 104.1±12.6, PDI = 96.9±15.0; nonsupplemented MDI = 105.1±11.2, PDI = 97.0±14.8). The power of detection of a three-point difference between the groups was 90%.[36]

These results differ from those recently published by Moffatt et al. in a study carried out in Canada.[37] In their randomized preventive trial, 283 infants were followed up to 15 months; half received an iron-enriched formula and half received normal formula. The groups were initially comparable in iron status, development, and social variables. Differences in iron status were observed at 9 to 12 months, with a reduction of anemia prevalence and iron deficiency. However, in contrast with the Chilean study,[36] the groups also displayed a psychomotor development score (PDI) difference. The nonsupplemented group showed a significant decrease in scores at 9 to 12 months, but the score spontaneously recovered at 15 months. No change was noted in mental development. The authors concluded that iron supplementation forestalled an albeit transitory drop in PDI scores and suggested the need for further study.

The results of the study being carried out in Chile only permit the conclusion that iron supplementation between 6 and 12 months did not improve MDI or PDI scores, and that differences in achievement noted between anemic and control groups at that age may be explained by factors other than anemia. There are some important methodologic differences which must be taken into account. First, the exclusion of anemic infants at 6 months introduced an important change in relation to the timing of iron deficiency. Anemia before 6 months of age may have affected the infants' CNS development in different ways during this higher-growth period. The score differences reported at 12 months may have corresponded to iron deficiency anemia that started before 6 months of age, and chronicity of the anemia may also have played an important role. Birth weight (>3000 g) may also have influenced the results by delaying the appearance of anemia or by providing the infant with an additional resilient component. A favorable genetic inheritance may promote sound prenatal development; this secure, resilient base may protect against possible adverse physical and psychologic postnatal factors in the postnatal period and beyond.[24] Finally, infants included in the preventive trial enjoyed a prolonged period of breastfeeding as a result of effective government policy. Data from recent studies suggest that prolonged breastfeeding has a beneficial effect on infant development and neurologic maturity.[38–42]

Possible Explanatory Mechanisms

Findings regarding the relationship between malnutrition and development—both in animals and humans—are partially applicable to the issue of the effects of anemia as a micronutrient deficiency. This similarity allows for the formulation of hypotheses which help understand the association between early anemia and psychomotor delay. Sources of information on biologic research offer insights into functional changes in the nervous system during periods of rapid brain growth.[43] A growing body of studies demonstrate the role of cerebral iron, especially in the myelination process.[5] Insufficient iron availability during periods of rapid incorporation of this nutrient into brain tissue that coincide with periods of myelination of nervous tissue may provide a physiologic explanation for observed behavioral changes. Experimental evidence also suggests that cerebral iron deficiency that occurs at an early stage persists into adult life, even after recovery from anemia during the first few months.[3] This may explain the CNS changes with maturity described by Peirano et al.[33,34]

Functional changes in the nervous system may provoke behavioral modifications that, through "functional isolation" (a concept derived from research in malnutrition),[44] help explain differences in achievement between iron-deficient anemic infants and others. Anemic infants, like infants suffering from malnutrition, demonstrated behavioral characteristics that limited their interactions with their physical and social environment. Lozoff et al.[7] and Walter et al.[26] reported emotional changes in task orientation among anemic infants. Lozoff et al.[30] also showed changes in mother-child interactions, with anemic infants remaining closer to their mothers and less interested in exploring their surroundings. Behavioral changes observed during the first 2 years of life persisted in the long term. Preschool children who suffered from iron deficiency anemia at 12 months were less active and attentive at play than their nonanemic peers.[45] These continuing characteristics may make their interactions with the environment more difficult. The behavioral and emotional patterns described above support the interpretation that anemic infants are functionally isolated and may explain the delay in their acquisition of motor and mental skills.

Following a similar approach, Pollitt[28] proposed that physiologic changes caused by malnutrition affect a child's behavior and thus change the course of normal development. Behavior is delayed but eventually reaches normal levels of development. Nutrition deficiencies that occur simultaneously with important milestones in motor development (standing, walking independently) may cause a slight delay in some motor behavior and may adversely affect cognitive development. Standing and walking independently change an infant's referential position in space, thus introducing new internal (proprioceptive and vestibular) and external (spatial organization) signals. Pollitt postulates that the attainment of new motor mechanisms triggers development events.[28]

Behavior and developmental changes observed in anemic infants are probably intensified by other environmental conditions that impair normal development. Anemia is more prevalent in poor populations, where iron in the diet is insufficient in relation to an infant's high demand. Likewise, it is probable that in poor families, biologic and environmental risk factors coexist.[24,46] Thus, it is unlikely that the observed differences in mental and motor development scores in anemic infants are the result of only one risk factor but, rather, are the consequence of a combination of several associated risk factors.

In conclusion, case-control studies clearly show an association between iron-deficient anemic infants and a decrease in mental and motor development index. This decrease is not observed in nonanemic iron-deficient infants. However, the studies do not yet allow for the formulation of a causal relationship, only an associative relationship. The preventive trial currently being carried out in Chile is in its final phase of data collection and analysis, and we hope to obtain relevant information soon. The study design will allow us to address such factors as the initial appearance of anemia and the reversibility of changes through a combination of oral iron treatment and a stimulation program to strength mother-child relationships. Neurophysiologic studies will allow a better understanding of the mechanisms involved in iron deficiency anemia and behavior.

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