NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH Public Access
Author Manuscript
J Dev Behav Pediatr. Author manuscript; available in PMC 2007 July 3.

Published in final edited form as:
J Dev Behav Pediatr. 2006 October ; 27(5): 371–378.

Iron Deficiency in Infancy and Mother-Child Interaction at 5 Years

FEYZA CORAPCI, Ph.D.,
Center for Human Growth and Development, University of Michigan, Ann Arbor

ANGELA E. RADAN, Ph.D., and
Hospital Nacional de Niños and University of Costa Rica, San Jose, Costa Rica

BETSY LOZOFF, M.D.
Center for Human Growth and Development and Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan

Abstract

Five-year-old Costa Rican children, who had either chronic, severe iron deficiency or good iron status in infancy, were observed with their mothers during a structured interaction task in a laboratory setting and everyday interactions in their home. Child affect and behavior as well as the quality of mother-child interaction of the formerly chronic iron-deficient children (n = 40) were compared to those with good iron status in infancy (n = 102). Children who had chronic iron deficiency in infancy were more likely to display lower levels of physical activity, positive affect, and verbalization during the structured task at 5 years, despite iron therapy that corrected their iron deficiency anemia in infancy. Mother-child reciprocity during the structured task (e.g., eye contact, shared positive affect, turn taking) was more likely to be lower in the chronic iron deficiency group compared to the good iron group. Mothers of children in the chronic iron deficiency group showed less responsivity in both settings. These results show that children with chronic, severe iron deficiency in infancy continue at behavioral disadvantage relative to their peers at school entry. Sustained differences in mother-child interaction might contribute to the long-lasting behavioral and developmental alterations reported in children with chronic, severe iron deficiency in infancy.

Keywords

iron deficiency; infancy; behavior; parent-child interaction; preschool age

---

Infants with iron deficiency anemia (IDA) or other evidence of chronic, severe iron deficiency (ID) show poorer mental, motor, and social/emotional functioning, on average, than infants with good iron status.[1,2] Although mental and motor findings have received the most attention, alterations in the social/emotional domain are among the most consistent results. Studies have found that infants with chronic, severe ID, compared to those with good iron status, are more likely to be fearful, hesitant/wary, unhappy, inactive, easily fatigued, in close contact with their mothers, or lower in vocalization.[3-9]

Such behavioral and affective alterations have been interpreted as evidence of “functional isolation”.[10] According to the functional isolation hypothesis, nutritional deficiencies contribute to changes in infants’ affect and activity, which in turn means that they are less likely to seek and/or receive developmentally facilitating interactions from their caregivers. Examples of such interactions include responsiveness, verbal stimulation, and encouragement of exploration. Combining the functional isolation hypothesis with recent research on ID and

---

Address for reprints: Betsy Lozoff, M.D., Center for Human Growth and Development, 300 N. Ingalls, Ann Arbor, MI 48109-0406; e-mail: blozoff@umich.edu.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

brain development, Lozoff and colleagues[11,12] have postulated that brain effects of ID (e.g., alterations in neurotransmitters, myelination, neurometabolism) and associated child behavioral/affective alterations operate in a transactional fashion with less stimulating parenting, thereby leading to a child's functional isolation from the environment and contributing to poorer behavioral and developmental outcomes over time.

Although there is growing empirical evidence regarding altered affect and behavior in infants with chronic and severe ID, research on parent-child interaction has been limited. To date, only two studies of iron-deficient infants have examined the quality of caregiving using direct observations of mothers and infants. During a play observation in a clinic testing room in a Guatemala study, mothers of infants with chronic, severe ID were less likely to spend time at a distance from them, less likely to break close contact, and more likely to reestablish close contact when the baby moved away.[8] In the infancy phase of the present longitudinal study on the effects of ID on behavior and development, 12- to 23-month-old Costa Rican infants and their mothers were observed during free play, mental and motor testing, and in the home.[9] There were several findings related to maternal behavior and mother-child interaction. Infants with chronic, severe ID maintained closer contact with their mothers during play as well as motor testing and showed less pleasure and delight. In addition, observations in the home showed that these infants were more likely to be carried by their mothers. Finally, mothers of infants with chronic, severe ID also showed lower levels of positive affect (i.e., smile, laughter) during developmental testing and free play.

The nature of mother-child interaction in relation to child's iron status has not been examined beyond infancy. Yet sustained differences in mother-child interaction are central to the transactional framework of the functional isolation hypothesis and suggest an important potential mechanism by which early affective and behavioral changes could have long-lasting effects. In fact, the early adolescent follow-up of the original Costa Rica cohort revealed that children who had been treated for severe, chronic ID in infancy were rated by their parents and teachers as displaying higher levels of anxiety/depression, social problems, and attention problems at 11 to 14 years of age.[13] Using observational data of this cohort at the 5-year follow-up, our study compared mother-child interaction between children who had been treated for chronic, severe ID in infancy and those who had good iron status before and/or after treatment. Based on the functional isolation hypothesis and past research, we predicted that 5 year olds with chronic, severe ID in infancy (henceforward referred to as the chronic ID group) would continue to show affective and behavioral alterations and that their mother-child interaction would be less developmentally facilitating.

METHODS

Participants

This study focused on the mother-child interaction aspect of the 5-year follow-up assessment in a longitudinal iron deficiency (ID) project. The original study involved 191 infants from an urban community near San Jose, the capital of Costa Rica. The community was predominantly working class, and parents averaged 8 to 10 years of education. Enrollment entailed door-to-door screening of the entire community and included all 12- to 23-month-old infants who had a birth weight ≥2.5 kg and a singleton term uncomplicated birth, were free of acute or chronic medical problems, and had normal physical examinations, no iron therapy after 6 months of age, and no i.m. iron treatment at any age. The infants enrolled in the study had no evidence of growth failure, other nutrient deficiencies, or high lead levels. Details of the original study have been published previously.[14]

Iron status in infancy was assessed by hemoglobin and three measures of iron status (transferrin saturation, erythrocyte protoporphyrin, and serum ferritin). Infant iron status ranged from ID

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

with moderate anemia to iron sufficiency. Moderate anemia was defined as hemoglobin ≤100 g/L and mild anemia was defined as hemoglobin 101 to 105 g/L. ID was defined as serum ferritin ≤12 μg/L and either erythrocyte protoporphyrin >100 μg/dL packed red blood cells or transferrin saturation ≤10%. Iron sufficiency was defined as hemoglobin ≥120 g/L and no abnormal iron measures. Infants with hemoglobin <120 g/L and any degree of ID (defined above) were given either i.m. iron (calculated to increase hemoglobin to 125 g/L) or 3 months of oral iron therapy in two daily doses (ferrous sulfate: 3 mg/kg), one of which was personally administered by project personnel. Infants with hemoglobin ≥120 g/L who were either ID or iron depleted (defined as serum ferritin <12 μg/L) also received oral iron treatment. All infants with iron deficiency anemia (IDA) corrected their anemia with iron treatment, with an average increase in hemoglobin of 37 g/L, indicating an excellent response to iron therapy. However, some infants still had biochemical alterations after 3 months of iron therapy (e.g., erythrocyte protoporphyrin >100 μg/dL packed red blood cells or transferrin saturation ≤10%).

The present study used the same iron status grouping approach as in previous reports of outcomes in this cohort beginning with the 5-year follow-up.[13,15] The grouping combined participants who had ID with moderate anemia in infancy and those with higher hemoglobin levels but continued abnormalities of iron status measures after iron treatment in infancy into a chronic, severe ID group. Since anemia is a late manifestation of ID and hemoglobin level reflects chronicity and severity once anemia develops, infants with moderate IDA had to have chronic, severe ID. Children with higher hemoglobin levels (>100 g/L) in infancy who still had biochemical evidence of ID after treatment also had indications of more chronic, severe ID (i.e., lower hemoglobin and higher free erythrocyte protoporphyrin at study entry than infants whose ID completely corrected). Furthermore, unmodified cow milk was typically introduced in the first few months of life, and ID was identified at 12 to 23 months in this sample. Thus, ID is likely to have been chronic and severe.

We compared the chronic ID group to children with good iron status in infancy. The good iron group consisted of infants who were iron sufficient at study entry in infancy and those with any degree of ID who became iron sufficient after iron treatment in infancy. At the 5-year follow-up, the children's iron status was excellent, comparable to that in the reference sample of 5- to 10-year-old US children who were free of ID in the Second National Health and Nutrition Examination Survey (NHANES II).[16] Table 1 summarizes the iron status measures in infancy (before and after iron treatment) and at 5 years. Mothers generally had good iron status, and only six of the mothers in the entire sample had IDA at the time of infancy evaluation.[9,17] Eighty-five percent of the original infant cohort (n = 163) participated in a comprehensive 2-day assessment for the 5-year follow-up.[15] The analyses of the present study involved 142 children with usable videotaped mother-child interaction sessions. Technical problems with the videotapes (e.g., poor sound and picture quality) and the failure of a few families to attend the second-day assessment when the videotaping took place accounted for missing data. Children who were videotaped and included at this follow-up did not differ in background characteristics from the 49 children from the infancy cohort who were not videotaped or could not be located for the 5-year follow-up. Regarding behavior in infancy, the only difference was that children videotaped at the 5-year follow-up spent a smaller proportion of the motor test in infancy at a distance from their mother, compared to children without a videotape or who could not be located. There were no other significant differences in behaviors related to spatial relations, activity, or infant affect.

The average age of the children at the follow-up was 60.3 months (SD = 1.1). There were 76 boys and 66 girls. Forty of these children were in the chronic ID group in infancy and 102 were in the good iron status group. The accompanying caregiver was the mother 95% of the time. Mothers' average age was 31.5 (SD = 5.2), and 87% of the children came from two-parent households. Table 2 presents descriptive data on the participating children and their mothers

NIH-PA Author Manuscript

according to the child's iron status in infancy. The proportion of males in the chronic ID group was higher than in the good iron status group (73% vs 46%, Pearson χ^2 (1, N = 142) = 8.06, $p < .01$). Otherwise, there were no statistically significant differences between the two groups with regard to background variables.

Parental signed informed consent for the study was obtained by the project pediatrician. The infancy and 5-year research protocols were approved by the Institutional Review Board of Case Western Reserve University, Cleveland, the ethics committees of the Hospital Nacional de Niños and the Ministry of Health, Costa Rica, and the Office for Protection from Research Risks, National Institutes of Health.

Procedure

The 5-year follow-up assessment included direct behavioral observations of mother-child interaction during a structured task, which was videotaped in a dedicated clinic room for later coding. The task required the child and his/her mother to copy a picture using an Etch-a-Sketch drawing toy, each controlling one dial.[18,19] The mother was instructed to give the child whatever help she thought appropriate for the Etch-a-Sketch task. In addition, the quality of mother-child interaction in everyday situations was assessed during an hour-long home visit (see below). Based on direct behavioral observation and a semistructured interview, an observer collected information about the quality and quantity of stimulation and support available to a child in the home environment. Finally, mothers responded to questionnaire measures to provide demographic information (e.g., age, education level, single caregiver family status) and report on their current symptoms of depressed mood.

Measures of Parent-Child Interaction

We considered developmentally facilitative mother-child interactions to entail positive affect, dyadic reciprocity, verbalization, and responsiveness, with little negative affect or harsh, restrictive parenting. The Parent-Child Interaction System (PARCHISY)[20] and the Early Childhood version of the Home Observation for Measurement of the Environment (EC-HOME)[21] were used in this study to assess developmentally facilitative mother-child interaction in a laboratory setting during the Etch-a-Sketch task and in the home during a naturalistic observation session, respectively.

The PARCHISY is an observational coding scheme with a 7-point Likert type (never to always) format for the assessment of child and maternal affect and behavior. In the present study, the child codes included positive and negative affect, activity level, and rate of verbalization during the Etch-a-Sketch task. The mother-child dyadic interaction was assessed with the reciprocity code that pertains to the degree of shared positive affect (i.e., co-occurring mother-child smiling or laughter), eye contact, and "conversation-like" turn-taking during the task. Finally, maternal behavior codes included positive and negative affect, positive control (e.g., use of praise, explanations), negative control (e.g., use of criticism, use of physical control of dials), responsivity toward the child (e.g., the immediacy of maternal response to child behaviors and verbalizations), and verbalization.

The PARCHISY has shown good reliability and validity in previous research.[22,23] Two undergraduate students from the University of Michigan were trained on coding parent-child interaction by the first author (F.C.) to an initial interobserver reliability criterion of intraclass correlation of .75 or above. Reliability checks were made throughout coding on a randomly selected 10% of the tapes. Levels of agreement remained at or above the initial levels.

The EC-HOME measures the quality and quantity of cognitive, social, and emotional stimulation available to a child at home. All items receive either a yes (1) or a no (0) score.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Previous research has established the HOME as a reliable and valid measure of the quality of caregiving behavior and family environment.[24,25] Following recent research,[26,27] items in the EC-HOME pertaining to maternal responsivity (10 items), stimulation (11 items), and avoidance of harsh parenting (six items) were summed to construct three composites of maternal behavior at home. Two trained Costa Rican psychologists reached satisfactory interobserver reliability (85% agreement). Neither the students nor the trained home observers were informed about participants' infancy hematologic status.

Other Measures

Maternal depression was assessed with the Spanish version of the Center for Epidemiological Studies-Depression (CES-D) scale.[28] The CES-D is a 20-item scale designed to assess current symptoms of depression in community samples. The respondents rate the frequency of 20 symptoms during the past week on a 4-point scale (0 = less than a day, 1 = 1–2 days, 2 = 3–4 days, 3 = 5–7 days), resulting in a possible range of scores between 0 and 60. The items of the scale include depressed mood, loss of energy, feelings of helplessness and hopelessness, and problems with sleep and appetite. A score of 16 is a widely used threshold for clinical depression.[28] The scale has been shown to have satisfactory reliability and validity with ethnic groups in the United States and internationally.[29]

Statistical Analysis

The PARCHISY codes for negative affect were excluded from analyses since only 8% of mothers and 4% of children showed any negative affect during the Etch-a-Sketch task. The distributions of the EC-HOME composite scores were examined for normality prior to analyses, and analyses were conducted using untransformed data. Child gender was included as a covariate in all analyses, given that a greater proportion of the chronic ID group was male. Five other demographic and family background variables (child and mother age, father absence in the home, maternal education, and maternal depression) were also considered as potential covariates based on theory and existing research relating these factors to the quality of mother-child interaction.[24,27,30-32] Ordinal logistic regression was used to assess the effect of iron group status on child, mother-child interaction, and maternal behavior PARCHISY codes because these codes were ordinal categorical scores.[33,34] The ordinal logistic regression models the logit of the cumulative probability as a linear function of the predictors. Comparisons of the EC-HOME scores between the chronic ID and good iron status groups were made using analysis of covariance. Both analyses controlled for child gender and any other demographic or family background factor(s) significantly correlated with a given outcome.

RESULTS

Child Behavior and Affect

The duration of the structured observation in a laboratory setting (the Etch-a-Sketch task) was similar for children in the chronic iron deficiency (ID) and good iron status groups (4.7 ± 1.9 minutes versus 4.7 ± 1.1 minutes). Table 3 presents the results of the ordinal logistic regression analyses for the Parent-Child Interaction System (PARCHISY) codes, with children in the good iron status group serving as the reference group. The iron status group was a significant predictor of child positive affect (odds ratio [OR] for higher rating 0.43, $p < .05$), physical activity (OR 0.31, $p = .01$), and verbalization (OR 0.39, $p < .01$), after controlling for gender. The odds of having a higher rating for positive affect, activity, and verbalization were 57%, 69%, and 61% lower, respectively, for children in the chronic ID group compared to children in the good iron status group.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Mother-Child Interaction Quality

Iron status was also a significant predictor of the PARCHISY reciprocity code (Table 3, OR 0.43, $p < .05$). The odds of having a higher rating for reciprocity (e.g., less mutual positive affect, eye contact, and turn-taking) during the Etch-a-Sketch task were 57% lower among mothers and children in the chronic ID group compared to the mother-child dyads in the good iron status.

Maternal Behavior

The odds of having a higher rating for the PARCHISY responsivity code was 50% lower among mothers in the chronic ID group compared to mothers of children in the good iron status, after controlling for gender and maternal education (Table 3, OR 0.50, $p = .05$). There was no statistically significant difference for positive affect, positive and negative control strategies, and verbalization before and after covariate adjustment.

In the home, mothers of children in the chronic ID group were also observed to be less responsive to their children in everyday activities. The group difference in the responsivity composite of the Early Childhood-Home Observation for Measurement of the Environment (EC-HOME) was statistically significant before and after covariate adjustment (Table 4, $p < .05$). Mothers of children in the chronic ID group were also found to display harsh parenting (e.g., physical punishment, restrictions, intrusiveness) more often than their counterparts. However, this group difference in the harsh parenting composite became a statistically suggestive trend after control for child gender and maternal education ($p = .10$). Group differences on the EC-HOME stimulation composite were no longer significantly different after controlling for gender, maternal education and father absence in the home ($p = .14$). Effect sizes (Cohen's d) were calculated to determine the magnitude of the difference between the two groups.[35] Effect sizes for EC-HOME codes ranged from 0.22 to 0.34, where 0.34 is considered a small to moderate-sized difference.

DISCUSSION

In this study, 5-year-old Costa Rican children, who either had chronic, severe iron deficiency (ID) or good iron status in infancy, were observed with their mothers in a laboratory setting and in their home. As noted above, the chronic ID group consisted of children with moderate iron deficiency anemia (IDA) in infancy and those with hemoglobin levels >100 g/L with continued abnormalities in iron status measure(s) after iron therapy. Despite correction of IDA with treatment and excellent iron status at 5 years, children in the chronic ID group were more likely to display lower levels of physical activity, positive affect, and verbalization during a structured interaction task, compared to children with good iron status in infancy. During the laboratory observation, mother-child reciprocity and maternal responsivity toward the child were also more likely to be lower in the chronic ID group. During everyday activities in the home, mothers in the chronic ID group were observed to be less responsive to their children than mothers in the good iron group.

We were unable to identify other studies of mother-child interaction years after ID in infancy. In fact, there are only a few studies that included direct observations of infant behavior and mother-child interaction during the period of ID. Those few studies point to altered caregiver behavior: mothers of infants with ID maintained closer proximity to their babies and showed less positive affect in their interactions.[8,9] The closer proximity may have been an appropriate response to the infant's affective alterations but, combined with less positive maternal affect, may have limited optimal social environmental input during infancy.[9] The present study indicates that certain characteristics of the mother-child interaction (e.g., the emotional tone of the mother-child dyad) were carried forward through the preschool period to 5 years, the

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

age at school entry. Less mother-child reciprocity (e.g., eye contact, mutual positive affect, and turn-taking) during a structured task in the laboratory setting and less maternal responsivity in both laboratory and home settings, which characterized mother-child interaction of the chronic ID group at 5 years, might have resulted through reciprocal, dynamic interactions between a wary, hesitant, solemn, or less active ID child and his/her mother over time.

Lack of warmth and responsivity in the mother-child dyad has consistently been shown to predict poor behavioral/developmental outcomes, either through its modeling effect or by setting a less nurturing context for subsequent mother-child interactions.[32] Contemporary theories of child development and a growing body of empirical evidence indicate that continuity in child developmental outcomes can, in large part, be explained by the continuity in the relationship between the child and the caregiving environment.[36-38] In a related fashion, the functional isolation hypothesis in the nutrition field postulates that altered transactional processes between child and caregiving environment sustain behavioral and developmental alterations in children who experience nutrient deficiencies in infancy and contribute to poorer outcome in the long term.[10,39-41] Follow-up studies to date have established that chronic, severe ID in infancy places children at risk of poorer cognitive and motor outcome years later.[13,42-50] This study shows that differences in child affect and mother-child interaction also persist for such children.

Several lines of research point to the importance of “child effects” as a starting point in the transactional processes in the case of ID in infancy. One piece of evidence is that the behavior of other adults was also different with chronic ID infants. In the infancy phase of the study,[9] the tester, a stranger who was uninformed about the infants’ hematologic status, responded differently toward IDA and comparison group infants during developmental testing. The tester offered fewer demonstrations and encouragements and ended the motor test sooner for the anemic group.

A second piece of evidence for child effects comes from large, randomized, controlled trials of the behavioral and developmental effects of iron supplementation in infancy. In a study of healthy, full-term infants, a greater percentage of the group who did not receive iron supplementation never smiled or interacted socially during a developmental assessment at 12 months, compared to infants who were iron supplemented between 6 and 12 months.[7] The groups were comparable in family background, including socioeconomic status and maternal depression, and infant temperament measured prior to supplementation was controlled. Another supplementation trial conducted in Bangladesh with infants at risk of stunting showed similar differences in social interaction.[51] With random assignment to iron supplementation or no added iron, these supplementation trials provide more convincing evidence that lack of iron in infancy causes alterations in infant affect and interaction, independent of child or family differences.

Further evidence of a causal effect of lack of iron on behavior comes from animal studies in which the environment is controlled and differences in iron status are experimentally induced. Studies in both monkey and rats document behavioral differences in infancy and later on that relate directly to findings in the human infant.[52] The first nonhuman primate model of experimental iron deprivation recently found that monkey infants on iron-deprived diets postnatally showed emotional withdrawal and hyper-emotionality. This behavior pattern was observed even though none of the monkeys had IDA.[52] Recent studies in rodent models of developmental ID show altered response to the unfamiliar in rats on iron-deficient diets. Such studies also identify plausible biological mechanisms for both short-term and long-lasting effects, especially related to neurotransmitter function and gene and protein profiling.[11]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Limitations

Altered transactional patterns between ID children and their mothers were detected in infancy during the period of ID[8,9] and again at age 5. However, we do not know exactly when children in the chronic, severe ID group corrected their iron status. They became comparable to the good iron group some time between the end of the infancy study and age 5, indicating that the Costa Rican diet was apparently adequate to correct the residual evidence of ID post-treatment in infancy. Given slower growth and more varied diet by late infancy, it is likely that the correction occurred early on rather than later.

Despite the accumulating evidence, the present study cannot prove that chronic, severe ID in infancy caused the observed affective and interactional alterations. It is possible that some factor(s) closely associated with ID might account for the group differences in infancy and at 5 years. For example, ID is often embedded in the context of less advantaged environment,[53,54] making the issue of contextual factors especially important. Maternal depression is one such factor that is particularly relevant to the focus of this observational study on mother-child interaction. Maternal depression could limit a mother's ability to provide optimal support for the child's development. There were no group differences in maternal depressive symptoms at the 5-year follow-up, and results remained significant after controlling for this variable. However, maternal depression was not measured in infancy.

Maternal nutritional status is another relevant factor that may affect child iron status and -rearing behavior. For example, in a recent study in South Africa, anemic mothers were observed to be less responsive to their infants and issue more negative statements in their interactions, compared to mothers who were not anemic or once-anemic mothers who had been treated for IDA.[55] In the present study, only six mothers had IDA during the infancy phase, but iron status during pregnancy, the immediate postpartum period, or at 5 years was unknown.[9,15] If the mothers of infants with chronic ID were more depressed and/or had IDA early on or the families were more stressed and overburdened in other ways, such problems could also have initiated the transactional cascade described above. Finally, infant temperament prior to becoming ID might also have shaped key socialization patterns.[56-59] Such factors are important to assess in future studies to consider as plausible rival hypotheses that might explain iron status group differences. It will also be important to integrate behavioral and neurophysiological data in future studies to help clarify the combined psychosocial and biological mechanisms for sustained affective and behavioral changes in children with chronic, severe ID in infancy.

The generalizability of our results is unknown in the absence of other long-term studies of ID in infancy and its role on social interaction. Furthermore, the present study was conducted with healthy full-term infants without other health or nutritional problems. Such a population was selected by design in order to assess the effects of chronic, severe ID without the confounding effects of malnutrition, infectious diseases, etc. Whether the long-term results obtained in this sample would generalize to children who live under less healthy conditions remains to be investigated.

Conclusions and Implications

In summary, this follow-up study of 5-year-old children who differed in iron status in infancy points to persisting differences in child affect and behavior as well as mother-child interaction associated with chronic, severe ID in infancy. Going beyond past research, our results also suggest that sustained differences in maternal behavior may contribute to the long-lasting effects of early chronic, severe ID on children's behavior and development. The consistency in findings of poorer outcome in children who had chronic, severe ID in infancy despite iron treatment in all available long-term studies implies that additional interventions may be needed to prevent long-term effects. Increasing caregivers' sensitivity to differences in the ID child's

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

emotionality and behavior might be a useful target point for intervention efforts. Longitudinal research with direct behavioral observations might identify additional aspects of the caregiving environment that might be amenable to interventions to prevent poorer trajectories of long-term outcomes for chronic, severe ID in infancy.

Acknowledgements

This research was supported by grants from the National Institutes of Health (HD14122 and a MERIT Award to Betsy Lozoff, R37 HD31606). We are grateful to all families who participated in the study and to the dedicated coders (Jessica L. Ordonez and Ramya G. Gogineni).

References

1. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131:649S–668S. [PubMed: 11160596]
2. Lozoff, B.; Black, M. Impact of micronutrient deficiencies on behavior and development. In: Pettifor, J.; Zlotkin, SH., editors. Nutrition-Micronutrient Deficiencies during the Weaning Period and the First Years of Life. Basel: Karger; 2003. p. 119-135.
3. Honig AS, Oski FA. Solemnity: a clinical risk index for iron-deficient infants. Early Child Dev Care 1984;16:69–84.
4. Williams J, Wolff A, Daly A, et al. Iron supplemented formula milk related to reduction in psychomotor decline in infants for inner city areas: randomised study. BMJ 1999;318:693–698. [PubMed: 10074011]
5. Oski FA, Honig AS, Helu B, et al. Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. Pediatrics 1983;71:877–880. [PubMed: 6856400]
6. Walter T, De Andraca I, Chadud P, et al. Iron deficiency anemia: adverse effects on infant psychomotor development. Pediatrics 1989;84:7–17. [PubMed: 2472596]
7. Lozoff B, De Andraca I, Castillo M, et al. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003;112:846–854. [PubMed: 14523176]
8. Lozoff B, Klein NK, Prabucki KM. Iron-deficient anemic infants at play. J Dev Behav Pediatr 1986;7:152–158. [PubMed: 3722390]
9. Lozoff B, Klein NK, Nelson EC, et al. Behavior of infants with iron deficiency anemia. Child Dev 1998;69:24–36. [PubMed: 9499554]
10. Levitsky, DA. Malnutrition and the hunger to learn. In: Levitsky, DA., editor. Malnutrition, Environment, and Behavior. Ithaca, NY: Cornell University Press; 1979. p. 161-179.
11. Lozoff B, Beard J, Connor J, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64:S34–S43. [PubMed: 16770951]
12. Lozoff, B.; Wachs, TD. Functional correlates of nutritional anemias in infancy and early childhood-child development and behavior. In: Ramakrishnan, U., editor. Nutritional Anemias. New York: CRC Press; 2001. p. 66-88.
13. Lozoff B, Jimenez E, Hagen J, et al. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000;105:E51. [PubMed: 10742372]
14. Lozoff B, Brittenham GM, Wolf AW, et al. Iron deficiency anemia and iron therapy: effects on infant developmental test performance. Pediatrics 1987;79:981–995. [PubMed: 2438638]
15. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991;325:687–694. [PubMed: 1870641]
16. Life Sciences Research Office. Assessment of the iron status of the U.S. population based on data collected in the Second National Health and Nutrition Examination Survey, 1976–1980. Bethesda, MD: Federation of American Societies for Experimental Biology; 1984.
17. Wolf AW, DeAndraca I, Lozoff B. Maternal depression in three Latin American samples. Psychiatry Epidemiol 2002;37:169–176.
18. Block, JH.; Block, J. The role of ego-control and ego-resiliency in the organization of behavior. In: Collins, WA., editor. University of Minnesota Symposium on Child Psychology. Hillsdale, NJ: Lawrence Erlbaum Associates; 1980. p. 39-101.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

19. Egeland, B.; Kreutzer, T. A longitudinal study of the effects of maternal stress and protective factors on the development of high risk children. In: Green, AL.; Cummings, EM.; Karraker, KH., editors. Life-span Developmental Psychology: Perspectives on Stress and Coping. Hillsdale, NJ: Lawrence Erlbaum Associates; 1991. p. 61-84.
20. Deater-Deckard, K.; Pylas, M.; Petrill, SA. The Parent-Child Interaction System (PARCHISY). London: Institute of Psychology; 1997.
21. Caldwell, BM.; Bradley, RH. Home Observation for Measurement of the Environment. Revised Edition. Little Rock: University of Arkansas; 1984.
22. Deater-Deckard K. Parenting and child behavioral adjustment in early childhood: a quantitative genetic approach to studying family processes. Child Dev 2000;71:468–484. [PubMed: 10834478]
23. Deater-Deckard K. Nonshared environmental processes in social-emotional development: an observational study of identical twin differences in the preschool period. Dev Sci 2001;4:1–6.
24. Bradley, RH. Environment and parenting. In: Bornstein, MH., editor. Handbook of Parenting. Vol. 2: Biology and Ecology of Parenting. Mahwah, NJ: Lawrence Erlbaum Associates; 2002. p. 281-314.
25. Bradley RH, Caldwell BM, Rock SL, et al. Home environment and cognitive development in the first 3 years of life: a collaborative study involving six sites and three ethnic groups in North America. Dev Psychol 1989;25:217–235.
26. National Institute of Child Health and Human Development, Early Child Care Research Network (NICHD ECCRN). Duration and developmental timing of poverty and children’s cognitive and social development from birth through third grade. Child Dev 2005;76:795–810. [PubMed: 16026497]
27. Bradley RH, Corwyn RF. Productive activity and the prevention of behavior problems. Dev Psychol 2005;41:89–98. [PubMed: 15656740]
28. Radloff L. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
29. Naughton MJ, Wiklund I. A critical review of dimension-specific measures of health-related quality of life in cross-cultural research. Qual Life Res 1993;2:397–432. [PubMed: 8161976]
30. Bornstein, MH. Parenting infants. In: Bornstein, MH., editor. Handbook of Parenting. Vol. 1: Children and Parenting. Mahwah, NJ: Lawrence Erlbaum Associates; 2002. p. 3-43.
31. Pettit GS, Bate JE, Dodge KA. Family interaction patterns and children’s conduct problems at home and school: a longitudinal perspective. School Psychol Rev 1993;22:401–418.
32. Dodge KA, Pettit GS. A biopsychosocial model of the development of chronic conduct problems in adolescence. Dev Psychol 2003;39:349–371. [PubMed: 12661890]
33. Rasmussen JL. Analysis of Likert-scale data: a reinterpretation of Gregoire and Driver. Psychol Bull 1989;105:167–170.
34. O’Connel, AA. Logistic Regression Models for Ordinal Response Variables. Newbury Park, CA: Sage Publications; 2005.
35. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. 2. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
36. Denham SA, Workman E, Cole PM, et al. Prediction of externalizing behavior problems from early to middle childhood: the role of parental socialization and emotion expression. Dev Psychopathol 2000;12:23–45. [PubMed: 10774594]
37. Patterson, GR.; Bank, L. Some amplifying mechanisms for pathologic processes in families. In: Gunnar, M.; Thelen, E., editors. Minnesota Symposium on Child Psychology. Hillsdale, NJ: Lawrence Erlbaum Associates; 1989. p. 167-210.
38. Sameroff A, MacKenzie MJ. Research strategies for capturing transactional models of development: the limits of the possible. Dev Psychopathol 2003;15:613–640. [PubMed: 14582934]
39. Wachs TD, Sigman M, Bishry Z, et al. Caregiver child interaction patterns in two cultures in relation to nutritional intake. Int J Behav Dev 1992;15:1–18.
40. Gardner, JM.; Grantham-McGregor, S. Pan American Health Organization, Tropical Metabolism Research Unit and the World Bank. Pan Nutrition, Health, and Child Development: Research Advances and Policy Recommendations. PAHO Library Cataloging in Publications Data; Washington, DC: 1998. Activity levels and maternal-child behavior in undernutrition: studies in Jamaica; p. 32-42.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

41. Saco-Pollitt C, Triana N, Harahap H, et al. The eco-cultural context of the undernourished children in a study on the effects of early supplementary feeding in Indonesia. Eur J Clin Nutr 2000;54(suppl 2):S11–S15. [PubMed: 10902982]
42. Palti H, Pevsner B, Adler B. Does anemia in infancy affect achievement on developmental and intelligence tests? Hum Biol 1983;55:189–194.
43. Palti H, Meijer A, Adler B. Learning achievement and behavior at school of anemic and non-anemic infants. Early Hum Dev 1985;10:217–223. [PubMed: 3987574]
44. Lozoff B, Jimenez E, Smith J. Double burden of iron deficiency and low socio-economic status: a longitudinal analysis of cognitive test scores to 19 years. Arch Pediatr Adolesc Med. In press
45. Antunes, H. Iron Deficiency Anaemia in Infants—A Prospective Neurodevelopment Evaluation. Lisbon: Faculty of Medicine, University of Portugal; 2004.
46. Algarin C, Peirano P, Garrido M, et al. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual systems functioning. Pediatr Res 2003;53:217–223. [PubMed: 12538778]
47. Dommergues JP, Archambeaud B, Ducot Y, et al. Iron deficiency and psychomotor development scores: a longitudinal study between ages 10 months and 4 years. Arch Fr Pediatr 1989;46:487–490. [PubMed: 2596947]
48. Hurtado EK, Claussen AH, Scott KG. Early childhood anemia and mild or moderate mental retardation. Am J Clin Nutr 1999;69:115–119. [PubMed: 9925132]
49. Wasserman G, Graziano JH, Factor-Litvak P, et al. Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. J Pediatr 1992;121:695–703. [PubMed: 1432416]
50. De Andraca, I.; Walter, T.; Castillo, M., et al. Nestle Foundation Nutrition Annual Report (1990). Vevey, Switzerland; Nestec Ltd: 1991. Iron Deficiency Anemia and Its Effects upon Psychological Development at Preschool Age: A Longitudinal Study; p. 53-62.
51. Black M, Baqui AH, Zaman K, et al. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. Am J Clin Nutr 2004;80:903–910. [PubMed: 15447897]
52. Golub MS, Hogrefe CE, Germann SL, et al. Behavioral consequences of developmental iron deficiency in infant rhesus monkeys. Neurotoxicol Teratol 2005;28:3–17. [PubMed: 16343844]
53. Lozoff, B. Considering environmental factors in research on nutrient deficiencies and infant development. In: Perman, JA.; Rey, J., editors. Clinical Trials in Infant Nutrition. Philadelphia: Lippincott-Raven Publishers; 1998. p. 203-218.
54. Pollitt E. Developmental sequel from early nutritional deficiencies: conclusive and probability judgments. J Nutr 2000;130:350S–353S. [PubMed: 10721904]
55. Perez EM, Hendricks MK, Beard JL, et al. Mother-infant interaction and infant development are altered by maternal iron deficiency anemia. J Nutr 2005;135:267–272. [PubMed: 15671224]
56. Bates JE, Pettit GS, Dodge KA, et al. Interaction of temperamental resistance to control and restrictive parenting in the development of externalizing behavior. Dev Psychol 1998;34:982–995. [PubMed: 9779744]
57. Lengua LJ, Kovacs EA. Bidirectional associations between temperament and parenting and the prediction of adjustment problems in middle childhood. J Appl Dev Psychol 2005;26:21–38.
58. Rothbart, MK.; Bates, JE. Temperament. In: Damon, W.; Eisenberg, N., editors. Handbook of Child Psychology: Vol 3: Social, Emotional, and Personality Development. New York: Wiley; 1998. p. 105-176.
59. Wachs, TD.; Kohnstamm, GA. The bidirectional nature of temperament-context links. In: Wachs, TD.; Kohnstamm, GA., editors. Temperament in Context. Mahwah, NJ: Lawrence Erlbaum Associates; 2001. p. 201-222.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Iron Status in Infancy (Before and After Iron Therapy) and at 5 Years

Iron Status Measures	Chronic ID (n = 40)	Good Iron (n = 102)
Pretreatment (12–23 mo)		
Hemoglobin (g/L)	98.3 ± 10.9	121.8 ± 10.1***
Erythrocyte protoporphyrin (g/dL red blood cells)	319.2 ± 174.1	102.1 ± 61.0***
Serum ferritin (g/L)	3.4 ± 2.4	9.4 ± 9.4***
Transferrin saturation (%)	9.4 ± 2.9	16.3 ± 6.9***
After 3 mo of iron therapy Hemoglobin (g/L)	125.5 ± 10	134.4 ± 8***
Erythrocyte protoporphyrin (g/dL red blood cells)	108.2 ± 39.7	55.5 ± 18.8***
Serum ferritin (g/L)	15.4 ± 11.4	28.2 ± 24.3***
Transferrin saturation (%)	19.0 ± 9.2	26.2 ± 11.0***
Age 5 yr		
Hemoglobin (g/L)	132.1 ± 8	136.9 ± 9**
Erythrocyte protoporphyrin (g/dL red blood cells)	49.8 ± 26.5	41.5 ± 18.7*
Serum ferritin (g/L)	20.8 ± 10.6	22.5 ± 13.1
Transferrin saturation (%)	20.8 ± 7.5	22.7 ± 7.3

ID, iron deficiency.

Values are mean ± SD.

* $p < .05$;

** $p < .01$;

*** $p < .001$.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Child and Family Characteristics at 5 Years by Iron Status Group in Infancy

	Chronic ID (n = 40)	**Good Iron (n = 102)**
Child sex (male)	73%	46%*
Child age (mo)	60.4 ± 2.0	60.2 ± 0.5
Maternal age (yr)	30.2 ± 4.8	32.0 ± 5.8
Maternal education (yr)	9.3 ± 2.6	9.9 ± 3.7
Single caregiver family	18%	12%
Maternal depression (CES-D)[a]	18.6 ± 10.5	16.3 ± 8.4
CES-D 16	38%	28%

ID, iron deficiency; CES-D, Center for Epidemiological Studies-Depression.

Values are mean ± SD.

Tests of statistical significance of the differences between the chronic iron-deficient and good iron status groups are based on the Student *t* test or χ^2 test.

[a]Comparable high levels of depression have previously been reported in mothers of young children, especially under economic stress.[17]

* $p < .01$.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 3

Iron Status in Infancy and Child and Mother Affect/Behavior During Structured Task at 5 Years

Observational Code	OR	95% CI	*p*
Child (PARCHISY)[a]			
Positive affect	0.43	0.22–0.86	**.02**
Activity	0.31	0.15–0.66	**.01**
Verbalization	0.39	0.18–0.81	**.01**
Mother-child interaction (PARCHISY)[a]			
Reciprocity	0.43	0.22–0.87	**.02**
Maternal behavior (PARCHISY)[b]			
Positive affect	0.65	0.33–1.30	.22
Positive control	0.66	0.33–1.34	.25
Negative control	1.28	0.19–1.45	.50
Responsivity	0.50	0.25–1.00	**.05**
Verbalization	0.55	0.27–1.14	.11

PARCHISY, Parent-Child Interaction System.

Reference group for chronic iron deficiency group is good iron status.

p values ≤ .05 are shown in bold.

Odds ratios (OR) and 95% confidence interval (CI) from ordinal logistic regression.

[a] Adjusted for gender.

[b] Adjusted for gender and maternal education for all codes, with additional covariates of father absence and maternal depression for the negative control code.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 4

Iron Status in Infancy and Maternal Behavior in the Home at 5 Years

	Chronic ID (n = 36)		Good Iron (n = 95)				
Observational Code	**Mean**	**SD**	**Mean**	**SD**	**F**	**Effect Size[a]**	**Covariates**
Maternal behavior (EC-HOME)							
Responsivity	5.76	2.1	6.55	2.53	4.46**	0.34	Gender, M education, F absence
Stimulation	8.36	2.04	7.86	2.44	1.91	0.22	Gender, M education, F absence
Avoidance of harsh parenting	3.68	1.26	4.09	1.27	2.99*	0.32	Gender, M education

ID, iron deficiency; EC-HOME, Early Childhood-Home Observation for Measurement of the Environment; M, mother; F, father. Sample size differed slightly from other analyses due to some missing data in EC-HOME.

[a]Effect size (in SD units) = difference between the means divided by pooled standard deviation. Effect sizes shown are adjusted for covariates.

*$p = .10$;

**$p < .05$.