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IRON DEFICIENCY AND INFANT MOTOR DEVELOPMENT

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Abstract

Background—Iron deficiency (ID) during early development impairs myelination and basal ganglia function in animal models.

Aims—To examine the effects of iron deficiency anemia (IDA) and iron deficiency (ID) without anemia on infant motor skills that are likely related to myelination and basal ganglia function.

Study design—Observational study.

Subjects—Full-term inner-city African-American 9- to 10-month-old infants who were free of acute or chronic health problems with iron status indicators ranging from IDA to iron sufficiency ($n = 106$). Criteria for final iron status classification were met by 77 of these infants: 28 IDA, 28 non-anemic iron-deficient (NA ID), and 21 iron-sufficient (IS).

Outcome measures—Gross motor developmental milestones, Peabody Developmental Motor Scale, Infant Neurological International Battery (INFANIB), motor quality factor of the Bayley Behavioral Rating Scale, and a sequential/bi-manual coordination toy retrieval task. General linear model analyses tested for linear effects of iron status group and thresholds for effects.

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CONFLICT OF INTEREST STATEMENT

No author has a conflict of interest.

Results—There were linear effects of iron status on developmental milestones, Peabody gross motor (suggestive trend), INFANIB standing item, motor quality, and toy retrieval. The threshold for effects was ID with or without anemia for developmental milestones, INFANIB standing item, and motor quality and IDA for toy retrieval.

Conclusions—Using a comprehensive and sensitive assessment of motor development, this study found poorer motor function in ID infants with and without anemia. Poorer motor function among non-anemic ID infants is particularly concerning, since ID without anemia is not detected by common screening procedures and is more widespread than IDA.

Motor development in infancy interacts with and affects several other domains, including perceptual, cognitive, and social-emotional development (1–3). One widespread condition that appears to impede the normal course of early motor development is iron deficiency (ID). In developing countries, over 50% of pregnant women are anemic (4), as are 46–66% of children under 4 years, with half attributed to ID (5).

Nine of 12 previous studies that assessed infant motor development using global tests reported lower motor scores in infants with iron deficiency anemia (IDA) compared to nonanemic infants (6). A few studies showed motor improvement after iron therapy, but all available follow-up studies reported long-lasting motor differences (see review (7)). Among randomized controlled trials of across-the-board iron supplementation (in contrast to iron treatment for infants with IDA/ID), 7 of 9 that assessed motor function reported benefits of iron (6). These global test results, though consistent, give little indication of specific central nervous system (CNS) effects of ID that are relevant to motor development.

Iron is involved in many CNS processes. Most relevant to motor function are documented effects of ID on myelination and basal ganglia function, especially related to the dopamine system (8). Based on such brain-behavior findings in rodent models and using a more comprehensive motor assessment than previous studies, this study tested the hypothesis that motor functions specifically related to myelination and/or basal ganglia would be affected by IDA in infancy. We further hypothesized that motor function would vary depending on the severity of ID, predicting that non-anemic iron-deficient (NA ID) infants would be intermediate between IDA and iron-sufficient (IS) infants. The final aim was to assess reversibility of effects with 3 months of oral iron therapy. We were not able to achieve this final aim, however, because there was uncertainty about adherence to treatment and more than 40% of the sample did not return for a post-treatment blood test (9). Given these uncertain and incomplete data on treatment, this report focuses on pretreatment findings. The study was part of an integrated cross-species (human, non-human primate, and rodent) program project on the brain-behavior effects of early ID.

METHODS

Sample

The study was approved by the Institutional Review Boards at Wayne State University and the University of Michigan, and signed informed consent was obtained from the infants' mothers. Infants were recruited from the General Pediatric Clinic of the Children's Hospital of Michigan, which serves an economically-stressed inner-city population. Participation was restricted to healthy, full-term singleton infants, born to mothers ≥ 18 years, with birth weight $> 5^{\text{th}}$ percentile, no perinatal complications, no maternal diabetes, emergency C-section, heavy alcohol use, or other incapacitating condition, not in foster care, and no chronic health problem or hospitalization more than once or for > 5 days. Since the clinic population was $> 90\%$ African-American, infants who were not African-American were not recruited. A total of 113 9- to 10-month-old infants participated in the neurobehavioral

study; 106 met criteria for initial iron status classification and 77 did so for the final classification (see below). Details of recruitment and attrition have been described previously (9;10).

Sample characteristics are described in Table 1. Infants weighed over 3.2 kg at birth on average, and slightly more than half were male. All infants received iron-fortified formula, with 40% initially breast-fed. Most mothers were single; 77% completed high school. The economically stressed nature of the sample is indicated by almost universal participation in the Women, Infants, and Children program, health care coverage primarily by Medicaid insurance, and relatively low scores for socioeconomic status.

Iron status

Initial venous blood tests included a complete blood count, lead, and zinc protoporphyrin/heme ratio (ZPP/H), performed at the Detroit Medical Center. Remaining blood was separated and frozen for subsequent determination of serum iron, total iron binding capacity, transferrin saturation, and ferritin. Assays were performed using standard techniques and strict quality control (11). To classify iron status, we used cutoffs from NHANES II (12), NHANES III (13), and CDC publications (14;15). Initial hematologic criteria were based on measures that were available for all infants within a few days: hemoglobin (HB), mean corpuscular volume (MCV), red cell distribution width (RDW), lead, and ZPP/H (missing for 4 infants). Infants were considered provisionally qualified based on the following criteria: at least one abnormal value among $MCV < 74$ fl (15), $RDW > 14.0\%$ (14), and $ZPP/H > 69$ $\mu\text{mol/mol}$ heme [corresponding to free erythrocyte protoporphyrin > 80 $\mu\text{g/dl}$] (12), with or without anemia ($HB < 110$ g/L), or clearly nonanemic ($HB \geq 115$ g/L) with normal MCV, RDW, and ZPP/H. There were 39 IDA, 45 NA ID, and 22 IS infants provisionally classified (total $n = 106$). For final iron status classification, ID was defined as 2 or more abnormal iron measures, with transferrin saturation $< 12\%$ (12) and ferritin < 12 $\mu\text{g/L}$ as additional abnormalities (13;14). IS was defined as $HB \geq 115$ g/L and no more than one abnormal iron measure. 77 infants met criteria for final classification (28 IDA, 28 NA ID, and 21 IS). Missing data were due to insufficient blood or technical problems. Table 2 shows iron status measures for provisional and final iron status classifications.

Assessment of motor development

The infants were assessed at the Child Development Research Laboratory, Department of Psychiatry and Behavioral Neurosciences, Wayne State University, by experienced examiners who were unaware of infant iron status. To consider effects of ID on myelination, we used several tests that are sensitive to overall motor delays (i.e., gross motor developmental milestones (16), Peabody Developmental Motor Scales (PDMS-2) (17), and Infant Neurological International Battery (INFANIB) (18). We also used a toy retrieval task to assess bi-manual coordination and sequencing of movements (19), skills developing during this age period that may depend on basal ganglia function (20–22).

Project personnel directly assessed gross motor milestones based on a pictorial milestone chart, ordered by age of expected achievement and ranging from sitting with support to running (16). The highest (most advanced) milestone was the major outcome analyzed.

Overall motor development was also assessed by the PDMS-2, a standardized test that measures gross and fine motor abilities from birth through 5 years of age. Gross, fine, and overall motor scores were the major outcomes. The examiner's general evaluation of motor performance was recorded on the motor quality factor of the Bayley Behavioral Rating Scale (BRS) (23).

Early neurological function was evaluated by the INFANIB (18), a neuromotor examination of reflexes, joints angles, and posture. Eight age-appropriate items were administered: scarf sign, heel to ear, popliteal angle, leg abduction, foot grasp, sideways parachute, backwards parachute, and weight-bearing during standing. Items were analyzed individually and as a sum.

A toy retrieval task specifically assessed bi-manual and sequential movements (19). Retrieving a toy from a translucent plastic box (20x12x6 cm) required a sequence of movements in which the infant's two hands were differentially activated: opening the lid with one hand and maintaining it in an open position against light pressure by the examiner, while reaching for the toy inside the box with the other hand and taking it out. Infants were videotaped during five 30-sec trials, with subsequent scoring by trained coders who reached reliability levels of 90–96%. The major outcomes were retrieval of the toy and performance with good bi-manual coordination. In good bi-manual coordination, the hand that retrieves the toy moves towards the body, while the other hand pushes the lid away from the body, so that the two hands act in opposite directions in a coordinated fashion.

Statistical analysis

All statistical analyses were performed using SAS 9.1 (24). For most motor outcomes, general linear model (GLM) analyses were used to test for linear effects (dose-response) of iron status group. To determine whether the threshold for effects was IDA or ID (with or without anemia), GLM analyses tested two preplanned contrasts: a) IDA vs. non-anemic infants (NA ID + IS) and b) ID (IDA + NA ID) vs. IS infants. The toy retrieval task, with its categorical outcomes, was analyzed by logistic regression utilizing generalized estimated equation (GEE) methodology (25).

Regarding covariates, there were no statistically significant group differences in birth or family background characteristics, regardless of whether the provisional or final iron status groups were compared. However, we controlled for any background factor that was even weakly correlated ($p < 0.10$) with a given outcome. Infant age and gender were initially considered in all models, as they may affect motor performance. Additional covariates were on conceptual grounds. Weight-for-height z-score was considered as a covariate for gross motor tasks, since it is possible that infants who are heavier for their length might have less muscle force relative to their size for gross motor movements. Hand size (the product of width X length) was considered as a covariate for fine motor tasks, since skills such as grasping could be influenced by object size in relation to hand size. Covariates that significantly contributed to the R^2 were retained.

RESULTS

Overall motor function

For gross motor milestones, there was a significant linear effect of iron status (controlling for weight-for-height z-score, which was the only significant covariate): IDA lowest, NA ID intermediate, and IS highest ($F(1, 67) = 4.6, p = .04$) (Fig. 1). The threshold was ID (with or without anemia) v. IS ($F(1, 67) = 4.33, p = .04$); the difference between NA ID and IS in pairwise comparisons was suggestive ($p = .06$). Only 19% of the IDA + NA ID infants could stand alone, whereas 34% of IS infants could do so and 19% were already walking alone.

On the Peabody Developmental Motor Scale (PDMS-2), there was a suggestive linear effect for gross motor scores. Scores for the NA ID group seemed to be intermediate between the IDA and IS groups ($F(1, 73) = 3.49, p = .07$), but the difference between NA ID and IS was not statistically significant. Age was the only significant covariate.

On the INFANIB, there was a linear effect for the standing item. More of the NA ID infants, compared to IDA infants, had normal adult-like weight bearing while standing, and the IS group had the highest percentage of such infants ($F(1, 70) = 4.80, p = .03$). The threshold was ID with or without anemia. ID infants, regardless of anemia, performed more poorly on the standing item compared to IS infants ($F(1, 70) = 5.30, p = .02$) (Fig. 2). NA ID was significantly lower than IS in pairwise comparisons ($p = .02$). Infant age and mother's age were the only significant covariates.

There was a significant linear effect of iron status on examiners' assessment of the general quality of motor performance, using the BRS Motor Quality factor ($F(1, 65) = 5.90, p = .02$). The threshold was ID (with or without anemia) v. IS; IDA and NA ID infants were rated as having poorer motor quality than IS infants ($F(1, 65) = 6.31, p = .01$) (Fig. 3). NA ID was significantly lower than IS in pairwise comparisons ($p = .01$). Infant age, mother's age, and maternal depression were the significant covariates.

Bi-manual coordination and motor sequencing

On the toy retrieval task, there was a significant linear effect of iron status on the quality of bi-manual coordination with the provisional iron classification and its larger sample size ($\chi^2(1, N = 105) = 3.83, p = .05$). The NA ID group was intermediate between the IDA and IS groups (Fig. 4). The threshold was IDA v. non-anemic; IDA infants were less able to retrieve the toy from the box with good bi-manual coordination ($\chi^2(1, N = 105) = 3.93, p = .05$), compared to NA ID + IS. Gender and age were the significant covariates, with boys doing better than girls.

DISCUSSION

This study examined the effects of IDA and ID without anemia on infant motor development by assessing motor skills that relate to brain areas and/or processes known to be altered by early ID, namely myelination and basal ganglia function, especially related to the dopamine system. Several tests that are sensitive to overall motor delays, which may be affected by impaired myelination, indicated linear effects of iron status, specifically, developmental milestones, Peabody gross motor (suggestive trend), INFANIB standing item, and the BRS Motor Quality factor. The threshold for the effects on developmental milestones, INFANIB standing item, and motor quality was ID with or without anemia, and scores for the NA ID group were significantly lower than the IS group. The toy retrieval task, where performance may depend on basal ganglia function, also showed linear effects of iron status, and the threshold for this effect was IDA. These results controlled for background factors that correlated with outcome. A few previous studies found motor effects of ID without anemia (e.g., (26;27)), but most did not (see review (7)). Our detection of such effects may be due to using a more comprehensive and more sensitive motor assessment.

We will first discuss how ID effects on impaired myelination and poor function of the basal ganglia could affect and impair motor performance. We will point to some limitations of our study and end with a suggestion for a future intervention, aimed at overcoming these effects.

Impaired myelination is one potential mechanism for ID effects on overall motor development. Iron is essential for oligodendrocyte function, which is crucial for myelin production. ID during gestation and lactation in the rat induces changes in myelin components (protein, cholesterol, phospholipids and galactolipids) and compaction in adulthood, despite an iron-sufficient diet beginning at weaning (8). In the human IDA infant, slower transmission in the auditory and/or visual systems, both short-term and years after iron therapy (28), suggests that effects of ID in infancy on myelination may be widespread and long-lasting. The corticospinal tract, in which motor commands traverse from the motor

and sensory regions of the cerebral cortex to the spinal cord, is not completely myelinated at birth and thus may be particularly vulnerable to early ID effects. Impaired myelination in the entire brain and especially the corticospinal tract may delay and/or alter the normal development and refinement of motor skills.

Another potential mechanism for the effects of early ID on motor development is through altered basal ganglia function. In rodent models of diet-induced ID during gestation and lactation, severe IDA reduced D₁ and D₂ dopamine receptor densities in the striatum (8), along with poor growth. To be more relevant to IDA in human infants, the rodent model in our program project produced ID with a more moderate level of brain ID than previous studies and avoided marked growth restriction (29;30). Even in the more moderate ID model, deficits in a natural grooming sequence that depends on striatal dopamine function were observed in adulthood, despite correction of IDA and normalization of brain iron content in all areas but the thalamus (29).

The basal ganglia play important roles in learning and execution of sequential movements (20) and also control of bi-manual coordination, through motor inhibition of contralateral movements (21). Thus, the difficulty ID infants showed on the toy retrieval task, which requires sequential movements during bi-manual coordination, may relate to ID-induced changes in striatal dopamine function.

Although postural control has not been traditionally considered a major function of the basal ganglia, a recent review emphasizes their important contribution to regulation of postural control (31). Other outcomes with a threshold of ID with or without anemia (developmental milestones and INFANIB standing) depend on postural control at this age. Postural control may be sensitive even to ID without anemia because it involves more than one CNS process impaired by ID (i.e., myelination and basal ganglia function).

The study is limited by small sample size, and results may not generalize to other populations. Uncertainty concerning compliance with iron intake and the high proportion of missing hematology data at 12 months mean that the study could not assess the ability of iron therapy to improve infant motor development.

In sum, using a comprehensive and sensitive assessment of motor development, this study found poorer motor function in ID infants with and without anemia. These findings were independent of family background, suggesting that poorer development was not due to family factors, such as lack of maternal stimulation and encouragement/attention. The observed effects of ID without anemia are particularly concerning, since ID without anemia is not detected by common screening procedures and is more widespread than IDA. The observed motor deficits in early ID are consistent with impaired myelination and oligodendrocyte function, both of which appear to be sensitive to developmental experience (32). Thus, future interventions for ID in infancy that include motor training or other environmental enrichment might help reduce long-term effects.

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Figure 1. Effect of iron status (final classification) on gross motor developmental milestones scores at 9 months. There was a significant threshold between ID (with or without anemia) and IS ($p = .04$), but the linear effect better represents the results.

Figure 2.

Effect of iron status (final classification) on INFANIB standing item at 9 months. The standing item of the INFANIB showed a significant linear effect ($p = .03$), but a threshold between the ID (with or without anemia) and IS groups better represents the results.

Figure 3. Effect of iron status (final classification) on BRS Motor Quality at 9 months. There was a significant linear effect ($p = .05$), but a threshold between the ID (with or without anemia) and IS groups better represents the results.

Good coordination (probability)

Figure 4.

Effects of iron status (provisional classification) on the quality of bi-manual coordination during the toy retrieval task at 9 months. There was a significant threshold between IDA and non-anemic infants ($p = .05$), but the linear effect better represents the results.

Table 1Sample characteristics¹

<i>N</i> ²	106
Infant	
Age, months	9.7 ±0.4
Gender, % male (<i>n</i>)	55 (58)
Birth weight, kg	3.25 ±0.4
Gestational age, weeks	39.7 ± 1.2
Breast-fed, % yes (<i>n</i>)	40(42)
Mother and family	
Maternal age, years	24.7 ±5.9
Maternal marital status (married), % (<i>n</i>)	12(13)
Maternal education, years	12.4 ± 1.4
Socioeconomic status ³	29.1 ±8.0
Maternal depressive symptoms ⁴	6.5 ±5.7
Maternal anxiety ⁵	34.4 ±9.6
Maternal alcohol intake (oz absolute alcohol/day)	0.02 ±0.08
HOME score ⁶	31.3 ±5.7
Life events ⁷	6.3 ±4.6
Social support ⁸	3.3 ±0.5

¹ Values are means ± SD or % (*n*) for categorical variables.

² *N* varies slightly due to occasional missing data for some measures.

³ Hollingshead Scale for Socioeconomic Status (33)

⁴ Beck Depression Inventory (34)

⁵ Spielberger State-Trait Anxiety Scale (Trait) (35)

⁶ Home Observation for Measurement of the Environment-Revised (36)

⁷ Life Experiences Survey (37)

⁸ Social Support (Cmic's adaptation of a scale by Henderson) (38)

Table 2

Iron status of study groups

Group	IDA		NA ID		IS	
	Provisional	Final	Provisional	Final	Provisional	Final
<i>n</i>	39	28	45	28	22	21
Hemoglobin (g/L) ^{a,b,c}	101.5(5.1)	101.9(5.3)	119.2(5.8)	119.0(5.3)	123.7(5.1)	123.2(5.1)
MCV (fL) ^{a,c}	73.1 (4.7)	72.1 (5.0)	75.0 (4.7)	73.8 (4.3)	78.5 (2.6)	78.8(3.3)
RDW (%) ^{a,c}	14.3(1.5)	14.8(1.4)	13.8(1.0)	14.2 (0.9)	13.0(0.7)	12.9 (0.8)
ZPP/H (μmol/mol heme) ^{a,b,c}	110.9(40.9)	119.0(38.2)	99.6 (54.0)	96.4(51.9)	57.8 (8.2)	70.0(23.4)
Transferrin saturation (%) ^b	21.6(8.2)	20.2 (9.0)	26.0 (10.2)	26.3(11.6)	24.8 (10.4)	24.8 (8.9)
Ferritin (μg/L)	38.5 (29.2)	34.2 (29.3)	35.4 (29.9)	34.6(32.3)	35.5 (24.7)	32.1 (21.5)
Lead (μg/dL)	2.3 (1.6)	2.4(1.5)	2.7 (2.3)	2.7(2.5)	2.4(1.1)	2.5(1.4)

Values are means (SD). Significant group differences based on the final iron status classification ($p < .05$) are indicated by superscripts as follows:

^a IDA differs from IS;

^b IDA differs from NA ID;

^c NA ID differs from IS. The significant differences based on the provisional iron status classification were the same as for the final classification, with one exception: NA ID and IDA groups did not differ in ZPP/H.