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Iron Deficiency Anemia in Infancy: Long-Lasting Effects on Auditory and Visual System Functioning

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ABSTRACT

Evoked potentials provide noninvasive measures of nerve transmission and CNS functioning. Auditory brainstem responses (ABR) and visual evoked potentials (VEP) show dramatic changes in infancy, largely as a result of progressive myelination. Because iron is required for normal myelination, pathway transmission in these sensory systems might be affected by early iron deficiency. We previously reported evidence to that effect: infants with iron-deficiency anemia (IDA) had slower transmission through the auditory brainstem pathway, uncorrected by iron therapy. To determine long-term effects, ABR and/or VEP of healthy Chilean children who were treated for IDA or were nonanemic in infancy were compared at approximately 4 y of age. Absolute latencies for all ABR waves and interpeak latencies (except I–III interval) were significantly longer in former IDA children. Longer latency was also observed for the P100 wave on VEP. The magnitude of differences was large—about 1 SD. These findings, with differences in latencies but not amplitudes, further support the hypothesis that IDA in infancy alters myelination and provide evidence that effects on transmission through the auditory and visual systems can be long lasting. Subtle changes in sensory pathway transmission might be an underlying mechanism for the derailment of other developmental aspects in early IDA. **(*Pediatr Res* 53: 217–223, 2003)**

Abbreviations

ABR, auditory brainstem response
VEP, visual evoked potential
IDA, iron deficiency anemia or iron-deficient anemic
HLM, hierarchical linear modeling
CCT, central conduction time

Neurophysiologic methodologies are noninvasive approaches that can provide information about the functional integration of the CNS. For example, dramatic decreases in latencies in auditory and visual evoked potentials in infancy are often used to index the overall intactness and maturation of the CNS. Progressively shorter latencies until adult levels are achieved are thought to reflect the increasing speed of transmission through sensory pathways, resulting in large part from increased myelination of the auditory and optic nerves and at the intracerebral level (1–5).

ABR represent the progressive activation of different levels of the auditory pathway: wave I is generated peripherally in the auditory nerve, wave III reflects the firing of axons exiting the cochlear nuclear complex, and wave V reflects an action potential generated by axons from the lateral lemniscus (6, 7). We recently reported the use of ABR to determine the effects of early IDA on the functional development of the auditory system (8). Six-month-old Chilean infants with IDA tended to show longer latencies than controls, indicating slower transmission through the brainstem portion of the auditory pathway. Differences became pronounced at 12 and 18 mo, despite iron therapy. Because iron is required for the functioning of several neurotransmission systems, myelination, and neuronal metabolic activity, different processes may relate to these lasting ABR abnormalities. However, the findings of differences in latency but not amplitude and more effects on the central (*versus* peripheral) portion of the auditory pathway appeared to be strong support for the hypothesis that impaired myelination was the explanation for the findings (8). This interpretation relied on basic research showing that a) iron is intimately involved in oligodendrocyte function and the associated production and maintenance of myelin (9–12); and b) the rapid decrease in ABR latencies in infancy is primarily caused by myelination (13–15).

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The framework of impaired myelination also led us to postulate that other systems that are rapidly myelinating in infancy would be affected by early IDA. The visual system is particularly interesting in this respect, as it also matures dramatically in infancy. VEP represent the brain's electrical activity for a defined time after a visual stimulus. The decrease in latency of the major VEP component (wave P100) in early childhood is a well-recognized indicator of functional maturation of the visual pathway, primarily involving myelination of the optic nerve (5) but also multiple synapses at other levels between the retina and the primary visual cortex. More precisely, the generation of wave P100 localizes in the lateral extrastriate cortex (area 18), with corresponding activations in areas V3, V3a, and adjacent middle occipital gyrus (16).

We report here a study of ABR and VEP in former IDA children and controls at approximately 4 y of age. Because ABR differences had still been apparent after a year of oral iron in infancy, it was unclear whether differences would persist or resolve over the next several years. Our observation that differences remained after an entire year raised the possibilities of permanent changes or delayed maturation. We expected that the visual system would also have been affected in infancy but had no basis for specific predictions about long-term effects.

METHODS

Subjects. The children in this follow-up study had participated in previous research in Chile on the behavioral, developmental, and neurofunctional effects of IDA in infancy in the context of a randomized controlled trial of preventing IDA. Detailed descriptions of the population and findings during infancy have been published elsewhere (8, 17). In brief, study participants were healthy full-term infants (birth weights $\geq$3.0 kg, no perinatal complications, and no acute or chronic illnesses). Infants were identified as having IDA at 6, 12, or 18 mo. Anemia was defined as venous Hb $\leq$100 g/L at 6 mo and $<$110 g/L at 12 and 18 mo. Iron deficiency was defined as two of three iron measures in the iron-deficient range [mean cell volume $<$70 fL, erythrocyte protoporphyrin $>$100 μg/dL red blood cells (1.77 μM), serum ferritin $<$12 μg/L) and/or an increase in Hb $\geq$10 g/L after 6 mo of iron therapy (18). These cutoffs for anemia and iron measures were based on the consensus of the hematologists of the project (T. Walter) and its External Advisory Committee (P. Dallman, F. Viteri, and R. Yip), who used normative data to determine approximately 2 SD from the mean for age (19–21). For each IDA infant, the next infant of the same age who was clearly nonanemic (venous Hb $\geq$115 g/L) was invited to join the study as part of the "control" group. Six-month-old infants were treated for 1 y with 15 mg/d of elemental iron as oral ferrous sulfate; infants identified at 12 or 18 mo were treated with oral iron (30 mg/d) for a minimum of 6 mo. Infants from the control group were also treated with iron to assure that they did not become iron deficient with advancing age in this setting where iron deficiency was widespread.

Between 1997 and 2000, evoked potential studies (ABR and VEP) were conducted for study children at preschool age. Of the available children who had been part of the earlier study (6, 12, and 18 mo IDA and control groups), we choose those who were still under 5 y of age. Overall, 11% declined further participation and 16% could not be located or had moved outside the region. ABR and VEP data were obtained from participating children. A total of 64 ABR and 80 VEP recordings of good quality, collected at average ages of 4.3 y and 4.0 y, respectively, were available for analysis. In all, 41 former IDA children and 43 controls had usable data. The research protocols in infancy and at follow-up were approved by the institutional review boards of the University of Michigan Medical Center, Ann Arbor, of INTA, University of Chile, Santiago, and of the Office of Protection from Research Risks, National Institutes of Health. Signed informed consent was obtained for each phase of the study.

The characteristics of children with ABR and/or VEP data in this follow-up are presented in Table 1. Former IDA children tended to be male, weigh slightly less at birth with a bit shorter gestation (even at term, with birth weights of 3.0 kg or more), and gain more weight between birth and 6 mo. Therefore, these factors were controlled for in analyses of evoked potentials. Weight gain between birth and 6 mo showed no statistically

Table 1. *Background characteristics**

Group	Former IDA	Control
	(n = 41)	(n = 43)
Age at ABR (y)	4.26 ± 0.10	4.32 ± 0.08
No.	29	35
Age at VEP (y)	3.89 ± 0.09	4.03 ± 0.08
No.	40	40
Gender (% male)†	63.4	44.2
Characteristics in infancy		
Birth weight†	3429 ± 59	3582 ± 67
Gestational age†	39.2 ± 0.2	39.6 ± 0.2
Growth at 6 mo		
Weight for age (z-score)	0.57 ± 0.14	0.44 ± 0.11
Length for age (z-score)	−0.17 ± 0.15	0.05 ± 0.13
Weight gain, birth to 6 mo‡	4765 ± 112	4408 ± 102
Iron measures in infancy§		
IDA detected at 6 mo, no.	10	10
Hemoglobin (g/L)	94.5 ± 1.6	124.3 ± 1.7
Erythrocyte protoporphyrin (μg/dL RBC)	201.6 ± 30.5	85.1 ± 6.3
Mean cell volume (fL)	66.3 ± 1.6	75.0 ± 0.9
Ferritin (μg/L)	7.1 ± 3.4	17.0 ± 3.3
IDA detected at 12 mo, no.	21	21
Hb (g/L)	102.2 ± 1.4	122.5 ± 1.9
Erythrocyte protoporphyrin (μg/dL RBC)	172.6 ± 21.3	80.1 ± 3.8
Mean cell volume (fL)	65.9 ± 0.9	75.4 ± 0.6
Ferritin (μg/L)	4.5 ± 0.7	19.0 ± 2.5
IDA detected at 18 mo, no.	10	12
Hb (g/L)	106.7 ± 1.0	126.6 ± 1.2
Erythrocyte protoporphyrin (μg/dL RBC)	144.4 ± 9.7	74.8 ± 3.9
Mean cell volume (fL)	69.7 ± 1.2	76.3 ± 0.9
Ferritin (μg/L)	7.7 ± 1.1	14.5 ± 3.0

* Values are means ± SE for continuous variables and percentages for categorical variables. Statistical significance was determined by t test or chi square. RBC, red blood cells.

† $p < 0.10$; ‡ $p < 0.05$.

§ By design, anemic and controls groups differed in hematologic status. All comparisons are statistically significant.

significant relation to any ABR or VEP parameter and was omitted in final analyses. Hematologic status at the time of identification as IDA or control in infancy is also shown in Table 1. Oral iron therapy corrected anemia in all but one of these children; only five of the controls met biochemical criteria for iron deficiency at any time in infancy.

Procedures. All ABR and VEP measures were obtained and processed without knowledge of whether a given child was former IDA or control. The children were studied while awake during the daytime. Both ABR and VEP recordings were carried out in a quiet, dimly lit, and electrically shielded room using an integrated Nicolet Compact Four machine (Nicolet Biomedical Instruments, Madison, WI, U.S.A.). ABR and VEP were recorded using silver-silver chloride disk electrodes placed according to the 10–20 International System as follows: a) for ABR, the active electrode was placed on the vertex (Cz) and the reference one on the earlobe (A1 or A2) ipsilateral to the stimulation; a third electrode placed on the forehead was used as a ground; b) for VEP, electrodes were placed on the Oz (positive), FPz (negative), and Cz (common reference) positions. Interelectrode impedance was kept below 5 kiloohms.

Using the same procedures as in infancy, ABR were performed with the child in the supine position, elicited monaurally, stimulating the ipsilateral ear with a series of square wave rarefaction clicks (0.1 ms) through TDH-39 headphones at 85 dB nHL. The ABR were recorded twice to ensure reproducibility. Results were stored for off-line analyses. The following parameters were determined for every response: absolute latency and amplitude for waves I, III, and V, and interpeak latencies I–III, III–V, and I–V.

For VEP, children were seated alone in front of a monitor at a distance of 100 cm and were asked to look at a red point located at the center of the screen. Pattern stimuli (10 min of arc checks) were generated by a black and white video monitor. Checks were reversed at a rate of 1.9 alterations per second; the duration of the stimulus was 100 ms and acquisition time was 250 ms. A total of 100 trials was obtained with automatic rejection of artifacts. The VEP were recorded at least twice to ensure reproducibility. The bioelectrical activity recorded at Cz was amplified, filtered (1 Hz to 100 kHz), and automatically averaged in the Nicolet C4 system. Results were stored for off-line analyses. The absolute amplitude and absolute latency for wave P100 were determined for each VEP response. Data on other waves were not recorded.

Statistical analysis. Analysis of covariance was used to determine differences between former IDA and control groups on continuous variables. Categorical variables were analyzed using χ^2.

To address the issue of irregular progression *versus* developmental arrest, we used HLM (22), using mean CCT (wave I–V interval) data from the infant ABR study (8) to extrapolate the expected values if the rate of change remained the same. HLM estimates "growth" trajectories and allows determination of differences between groups in the parameters of the curves (*e.g.* base state, the linear change over time, the rate of change). In a two-level HLM analysis, level one provided parameters of change using an asymptotic model of decay. The asymptote was based on the observed mean CCT value of the nonanemic control group in the follow-up, and the value at birth was obtained from standard sources (4, 23). Level two of the model tested for significant differences in the change parameters between anemic and nonanemic groups, controlling for gestational age and birth weight. Gender was considered initially, but there were no significant differences ($p = 0.38$). HLM analyses were repeated using the values observed at 4 y to revise the projections and predict the rate of change in the future.

The exploratory nature of the HLM analyses should be noted. There were no local norms for values at birth or adulthood, and only 13 ABR records were from children who had ABR in infancy (eight identified at 6 mo and five at 18 mo). Thus, the extrapolation depended on infancy data from children who could not be part of this follow-up because they were already over 4 y of age. To consider the validity of the latter aspect, we first compared the ABR and VEP values for preschool-aged children with or without infancy data. There were no differences on any parameter.

RESULTS

Table 2 shows the mean and SEM for ABR and VEP, controlling for relevant background factors (age at testing, birth weight, gestational age, and gender). For ABR parameters, former IDA children had significantly longer latencies for all waves and all wave interpeak intervals except interval I–III. There were no differences in amplitude. For VEP, the latency of wave P100 was longer in former IDA compared with control children. Again, there was no difference in amplitude.

Figure 1 shows the magnitude of differences, expressed as effect sizes. Effect size is calculated as the difference between group means divided by the overall SD. Effect sizes for latencies were generally large to very large for ABR (about 0.8–1.2 SD units) and very large for VEP (1.2 SD unit).

To determine whether differences between the former IDA and control groups varied depending on age at diagnosis of IDA in infancy, we repeated the analyses of covariance adding this factor. There were no significant main effects of age at diagnosis or interactions. Regardless of the age in infancy when IDA was detected, there were statistically significant differences between former IDA children and controls in the latencies of ABR waves I, III, and V and of wave P100. Differences in interwave intervals showed the same pattern at suggestive levels of statistical significance ($p \leq 0.10$) with the added covariate.

In additional analyses of the ABR data to determine whether the more central or more distal components of the auditory pathway were differentially affected, we compared former IDA and control children on the central-to-peripheral ratio (wave III–V interval divided by wave I–III interval) (13), controlling for the background factors noted above. The central-to-peripheral ratio was higher in former IDA children (0.90 ± 0.02 *versus* 0.83 ± 0.02 in controls, $F_{1, 58} = 7.01$, $p = 0.01$).

We also sought to determine how the observed values for CCT compared with those projected using HLM techniques (Fig. 2). From an estimated common starting point at birth, significant differences between IDA and control groups were

Table 2. *Evoked potentials**

Group	Former IDA	Control	Significant background variables
Auditory Brainstem Responses at 85 dB			
No.	29	35	
Absolute latencies (ms)			
Wave I†	1.64 ± 0.02	1.51 ± 0.02	
Wave III†	3.78 ± 0.03	3.63 ± 0.02	
Wave V†	5.70 ± 0.03	5.40 ± 0.03	Gestational age, testing age, gender
Interpeak latencies (ms)			
Wave I–III interval	2.14 ± 0.02	2.12 ± 0.02	
Wave III–V interval†	1.92 ± 0.03	1.75 ± 0.03	Gender
Wave I–V interval (central conduction time)†	4.06 ± 0.03	3.87 ± 0.03	Gestational age, testing age, gender
Amplitudes (μV)			
Wave I	0.57 ± 0.04	0.56 ± 0.03	Birth weight
Wave III	0.51 ± 0.03	0.54 ± 0.03	
Wave V	0.55 ± 0.03	0.57 ± 0.03	Gender
VEP			
No.	40	40	
P100 latency (ms)†	104.7 ± 0.7	97.3 ± 0.7	
P100 amplitude	19.1 ± 1.3	21.5 ± 1.3	Testing age

* Values are adjusted means ± SE, controlling for gender, birth weight, gestational age, weight gain from birth to 6 mo, and age at testing. Statistical significance was determined by analysis of covariance.

† $p < 0.001$.

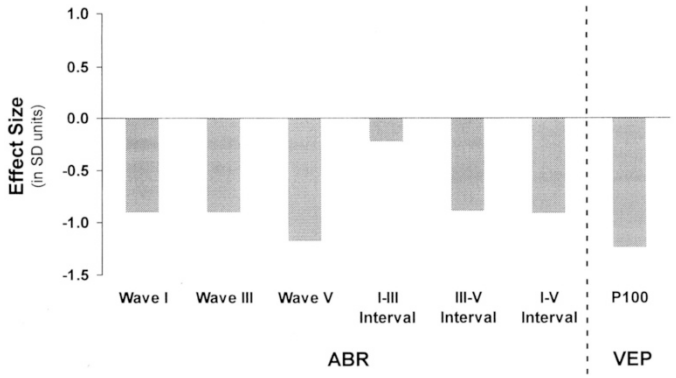

Figure 1. Magnitude of differences in evoked potential latencies between former IDA children and controls. Effect size is calculated as the control group mean minus the mean for former IDA children divided by the overall standard deviation. See Table 2 for levels of statistical significance.

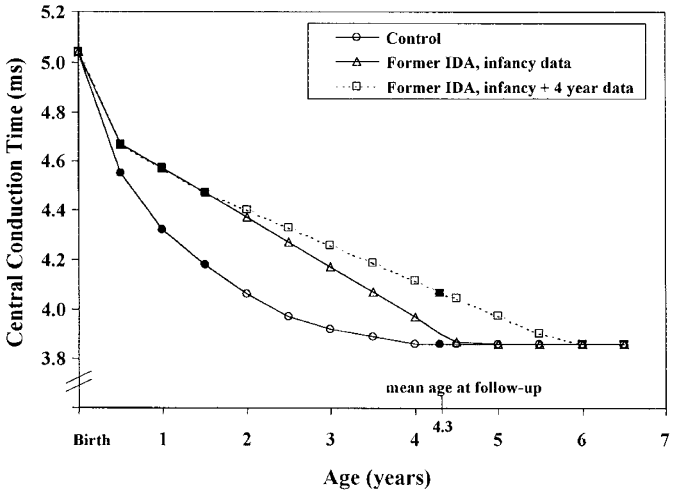

Figure 2. Projected rates of change in CCT. These curves are derived from HLM analyses. The *bottom curve* shows the pattern projected for the control group. The *middle curve* projects values for the former IDA group based on infancy data alone. The *top curve* shows the projection for former IDA children revised to include the observed value at 4.3 years. Points with *solid black symbols* are based on actual observations, and points with *open symbols* are estimated.

observed in the amount of change by 6 mo ($p = 0.02$) and the rate of change over time ($p < 0.01$). These differences combine to project significantly different times for reaching the asymptotic level ($p < 0.01$). Based on the rate of change observed at the end of the infancy study, the projection indicated that the nonanemic control group reached the observed value of 3.86 ms before the follow-up, with virtually all change completed by 24 mo (Fig. 2, *bottom curve*). ABR maturation in the control group thus appeared to correspond to that published for normally developing children. Projecting the rate of change observed in infancy for the former IDA group, however, showed that the CCT expected at 4.3 y (the average age at testing) was 3.89 ms (middle curve in Fig. 2). The value actually observed was 4.07 ms—a latency longer than predicted by approximately 1 SD. When HLM analyses were repeated using the additional observations from 4.3 y, the nonanemic trajectory changed little (and only one is graphed in Fig. 2). In contrast, the new projection for the former IDA group showed a drop significantly slower than that using the infancy data alone ($p <$ 0.01) and predicted a much later time for achieving the asymptote ($p < 0.01$). The revised projection (uppermost curve in Fig. 2) predicts that former IDA children will not reach the level of the control group until approximately 6 y of age.

DISCUSSION

The present study shows that ABR and VEP latencies were consistently longer in former IDA children relative to nonanemic controls, with differential effects on the more central portion of the auditory pathway. Differences in amplitudes were not statistically significant. Differences at follow-up were noted regardless of the age in infancy at which IDA had been

detected and despite iron treatment that corrected anemia in infancy for all but one child. The magnitude of effects on latencies was generally large—approximately 1 SD, the same magnitude observed for ABR in infancy. These findings provide the first evidence that effects of IDA in infancy on pathway transmission in both the visual and auditory systems can be long lasting.

The formation of fully mature myelin is a process that takes months or even years (24, 25), and it is thus plausible that the effects of a developmental insult might be observed later on, even if the apparent cause were treated. Furthermore, a primary role of oligodendrocytes is myelin production, and oligodendrocytes depend on iron availability for normal function. During development, disruption in the availability of iron has been shown to impede myelination (26). These developmental features might help explain our findings, especially when considering the region-specific fashion of the temporal sequence of myelination during childhood and adolescence (25). Differences in latency but not in amplitude in former IDA children support the hypomyelination hypothesis. It is generally accepted that latency changes relate to increases in conduction velocity during axonal myelination (13–15), whereas modifications in amplitude and duration are probably the result of improvements in synchronization at the axonal or synaptic levels (27). However, we emphasize that this study did not directly demonstrate delayed myelination. Anatomic neuroimaging would be required for this purpose.

Other relevant human studies of IDA are scarce and provide little comparable information. In a previous study in China, ABR abnormalities were noted in >50% of a group of 48 IDA infants (age range, 6 mo to 3 y); more severely anemic children had more severely disrupted ABR patterns (28). Reevaluation after iron therapy was performed only in four cases, with no clear pattern of results. In another study, in Turkey, ABR were also assessed in a group of infants averaging 14 mo of age (20 IDA, 20 controls), with repeat evaluations for the IDA group after 3 mo of iron therapy (29). No ABR differences between IDA and control infants were observed before treatment, but the expected developmental progression in ABR was not observed upon repeat assessment of IDA infants. Methodologic differences may account for the differences in findings between the Turkish study and our earlier ABR study. Infants in that study were evaluated under sedation, whereas our ABR assessments were performed without sedation during a spontaneously occurring nap. The age range was much wider (7–24 mo *versus* 6 mo in our study), and the time interval to reassessment was much shorter (3 mo *versus* 6 and 12 mo). The Turkish study also obtained VEP, but only in the IDA infants (again under sedation) before and after 3 mo (30). Without VEP in a control group, no pretreatment comparisons were possible. After 3 mo, the latency of a negative VEP component (N2) decreased, but it is not clear whether this change was the result of iron therapy or developmental progression. No study has evaluated long-term effects.

In animal models, there is evidence that early IDA effects on myelination are not reversed with iron therapy. In the developing rat with iron deficiency, cytological studies show that oligodendrocytes appear "immature" and do not revert to normal after treatment (31). An insult to the sensory receptor should also be considered. The only set of experimental studies of auditory functioning in developing rats found an auditory threshold elevation of >15 dB in about one third of the animals with severe IDA (32) and sudden sensorineural hearing loss in a few (33). The effects were specific to iron deficiency rather than anemia. Despite these suggestive studies, the mechanisms for long-lasting IDA effects are still unknown. However, some studies have reported long-term effects on ABR in other early biologic risks, such as lead exposure (34, 35) and generalized undernutrition (36, 37), suggesting the fruitfulness of characterizing the underlying processes in a variety of insults or stressors to the developing brain.

The impact of early IDA on the functional maturation of the auditory system was still apparent in the present study despite an overall decrease in average latencies for most ABR parameters for both former IDA and control groups at preschool age. The HLM projections of CCT indicate that the control group probably followed the normal developmental time course. In contrast, developmental change in the former IDA group was slower than predicted by the rate of change observed at the end of the infancy study. Former IDA children had not achieved the level of maturity in CCT that would be expected, even if they simply maintained the course established in infancy. In fact, the revised projection incorporating the observed 4-y data (Fig. 2, *top curve*) indicates that the former IDA group will lag behind the control group for approximately another 2 y. The HLM results thus suggest that auditory transmission was slower in the former IDA group throughout early childhood.

Relation to broader differences in behavior and development. Differences in functioning of both the visual and auditory systems make it plausible that there might be a generalized impact of IDA on myelination. Impaired myelination may help explain differences in broader behavioral systems reported in other studies of iron deficiency in infancy (reviewed in ref. 38). Differences in motor development are certainly relevant in this context, as the direct and important role of myelination in early motor development is well established. Several studies have found lower motor test scores in IDA infants (see ref. 38). Of the few randomized trials of the behavioral and developmental effects of iron supplementation, those with assessments in the first year of life generally reported motor effects (17, 39, 40).

Subtle alterations in auditory and visual processing could also contribute to specific cognitive outcomes reported in studies of early IDA (41). Longer ABR and VEP latencies might delay or disrupt the timing of input for other systems. In considering this line of reasoning, it should be recalled that altered myelination is not the only defect in early iron deficiency that might affect sensory processing. For instance, recent studies continue to document the alteration of dopaminergic functioning in iron deficiency (42). Dopamine neurotransmission has specific roles in circuits involved in transmitting visual and auditory information (43). In this context, altered dopaminergic function could disrupt the normal progression of fine-grained mechanisms of synchronization, including intermodal integration, inasmuch as connections might not be in place or fully functional at the expectable time (44).

Delays in the maturational process or altered timing for achieving specific neurofunctional developmental patterns of the visual and auditory sensory systems could affect the development of higher-order cognitive and emotional functions. Adequate development and functional integrity of both auditory and visual systems are important in assuring the structural and functional foundations for many learning processes. We speculate that the above-mentioned factors contribute to behavioral and cognitive alterations that have been reported in former IDA children (45–47). Relevant mechanisms might include hypomyelination of both auditory and visual sensory pathways, alteration of neurotransmission systems, delayed and/or asynchronous maturation of the neural interactions among different sensory modalities, and decreased neuronal metabolic activity (48). These mechanisms might act directly, influencing brain structure, biochemistry, and functional development, or indirectly, modifying the neural integration that defines brain development. Moreover, these mechanisms are not mutually exclusive and might act synergistically to induce altered function.

We did not test whether the altered evoked potentials actually resulted in abnormal visual or auditory function. Further large-scale longitudinal studies are needed to reveal the clinical significance of the observed alterations in evoked potentials. However, the changes we noted could be relevant to some specific behavioral/developmental outcomes in other studies of early iron deficiency in the human. For instance, IDA infants showed evidence of slower processing of visual information (longer looking times). Looking time—considered a fundamental cognitive property reflecting efficiency of information processing (49, 50)—predicts later IQ better than global tests of infant development (51, 52). Two other studies found that 5- to 51/2-y-old children who had had chronic, severe iron deficiency in infancy showed marked differences in visual-motor integration, perceptual speed, and/or motor proficiency (45, 46). In a follow-up at 11–14 y, such children showed poorer spatial memory and longer tachistoscopic threshold (the minimum time to perceive a difference in stimuli) and did not display the expected developmental shift in selective recall (47). Such findings appear compatible with disruptions in sensory processing and/or intermodal integration.

Limitations. It should be emphasized that our consideration of ABR results at preschool age in relation to patterns in infancy relies on group means only, because there were longitudinal data for only 13 children. Nonetheless, finding no differences on any ABR or VEP parameter among preschool-aged children who did or did not have infancy data suggests that those in the infant study were not atypical and that the rest of the sample can be considered a quasi-replication or internal confirmation of the results for children with longitudinal observations. However, the fact that we did not observe an effect of age at diagnosis of IDA does not mean that timing is unimportant. Our data only encompass the relatively narrow window of 6–18 mo. This period is largely after the exponential phase of ABR and VEP maturation. IDA occurring earlier (during the period of exponential change) or later (after maturation is largely complete) might well have different effects. Therefore, according to the timing of myelination and synaptogenesis within sensory pathways, one might expect greater ABR or VEP alterations in infants diagnosed as IDA at 6 mo of age. However, it is also conceivable that plasticity and recovery might be more possible earlier on.

CONCLUSION

In conclusion, IDA during infancy seems to induce mild auditory and visual dysfunctions that are long lasting. We suggest that these insults may act synergistically to disrupt the timing of key steps in CNS development, thus derailing the normal progression of neurofunctional maturation. Sustained during early development, these functional effects may limit the benefits conferred by environmental stimulation and contribute to long-lasting alterations in cognition and behavior among former IDA children.

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