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In utero Iron Status and Auditory Neural Maturation in Premature Infants as Evaluated by Auditory Brainstem Response

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Abstract

Objective—To determine if cord ferritin (CF) concentration, an index of *in utero* iron status, is associated with auditory neural maturation in premature infants.

Study design—A prospective cohort study was performed to compare auditory neural maturation between infants with latent iron deficiency (CF 11–75 ng/ml) and infants with normal iron status (CF > 75 ng/ml) at birth. Our inclusion criteria were 27–33 weeks gestational age infants admitted to the Neonatal Intensive Care Unit between July, 2007 and November, 2008 within 12 hours after birth and had cord blood collected. Infants with TORCH infections, chromosomal disorders, cranio-facial anomalies, culture proven sepsis, and/or unstable conditions were excluded. CF concentrations were measured using a chemiluminescence immuno-assay method. Bilateral monaural auditory brainstem evoked responses (ABR) were performed using 80 dB nHL click stimuli at a repetition rate of 29.9/sec within 48 hours after birth.

Results—Of 80 infants studied, 35 infants had latent iron deficiency. After controlling for confounders, infants with latent iron deficiency had significantly prolonged absolute wave latencies I, III, and V and decreased frequency of mature ABR waveform compared with infants with normal iron status.

Conclusion—Premature infants with *in utero* latent iron deficiency have abnormal auditory neural maturation compared with infants with normal *in utero* iron status.

Keywords

Auditory brainstem evoked response; latent iron deficiency; cord ferritin; brain development

Iron is crucial for fetal brain development and substantial iron accretion occurs during the last trimester of pregnancy.(1–5) Although there is active transport of iron across the placenta, several clinical conditions are known to negatively affect fetal iron status including severe

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maternal iron deficiency, intrauterine growth restriction, pregnancy-induced hypertension, maternal smoking, and maternal diabetes mellitus.(1,2,6–12) Iron deficiency during the critical period of brain development affects multiple developmental processes including myelination, dendritic growth, synaptic function, monoamine metabolism, and energy metabolism.(4,7, 13,14)

Cord ferritin (CF) concentration, a measure of tissue iron stores, is currently considered the best indicator of *in utero* fetal iron status, and remains the most widely used measure of iron status for neonatal outcome studies. (15–17) Neonatal observational studies suggest that latent or brain iron deficiency during *in utero* life as evaluated by CF concentration is associated with long-term adverse effects on the developing brain in near-term and term infants. (16,17) However, no data exist regarding acute concomitant effects of *in utero* latent iron deficiency on the developing brain in premature infants.

Auditory brainstem evoked response (ABR) is a non-invasive neurophysiologic assessment of auditory neural maturation, a surrogate outcome for brain maturation, in premature infants. (5,18,19) The ABR waveform in term neonates is comprised of 3 waves (I, III, and V). (19) Wave I is generated peripherally in the auditory nerve.(20) Wave III reflects the firing of axons exiting the cochlear nuclear complex in the brainstem, and wave V primarily reflects an action potential generated by axons from the lateral leminiscus at a more rostral brainstem location. (20) There is a rapid maturation of the ABR during the perinatal period that is influenced by the degree of myelination, neuronal development, synaptic function, and axonal growth in the auditory nervous system.(19,21) With increasing gestational age (GA), maturation of the ABR waveform is characterized by improving detectability of the response peaks and shortening of the absolute wave latencies.(19) The decrease in wave I latency reflects the maturation of the auditory pathway at auditory nerve level, and the decreases in waves III & V latencies reflect the maturation of the auditory pathway at the brainstem level.(20) Since waves I, III, & V are not always detectable in premature infants ≤ 33 weeks GA, the ABR waveform can also be categorized as a Response Type based on the replicability of the response and the presence of wave III or wave V.(19) The Response Type also demonstrates progressive maturation with increasing GA.(19) Therefore, categorization of the ABR waveform provides a useful approach and has been previously used to evaluate effects of perinatal factors on auditory neural maturation in extremely premature infants. (18,22) ABR has also been previously used to study effects of iron deficiency anemia in infants more than 6 months old. (23) This study seeks to determine if *in utero* iron status influences auditory neural maturation in 27–33 weeks GA infants.

METHODS

A prospective cohort study comparing auditory neural maturation of premature infants with latent iron deficiency (CF 11–75 ng/ml) with premature infants with normal iron status (CF > 75 ng/ml) was conducted. We chose a cord ferrtin concentration of 75 ng/ml as a cut off level to define latent iron deficiency because this cut-off level has been used by previous studies and was shown to be associated with neurodevelopment outcomes in term and premature infants. (15,17) Parental consent was obtained for each subject enrolled in the study. The study was approved by the Institutional Human Subject Review Board.

All infants 27–33 weeks GA at birth who were delivered and admitted to the Neonatal Intensive Care Unit (NICU) of University of Rochester Medical Center (URMC) between July, 2007 and November, 2008 were eligible for the study if cord blood was collected at the time of delivery. Infants with craniofacial anomalies, chromosomal disorders, TORCH infections (toxoplasmosis, other infections, rubella, cytomegalovirus infection and herpes simplex),

culture proven sepsis, or those who were too clinically unstable for ABR testing between 24–48 hours after birth were excluded.

GA was assessed by obstetrical dating criteria, or when obstetrical data was inadequate, by Ballard exam. Data were prospectively collected on demographics, maternal diabetes, pregnancy induced hypertension, chorioamnionitis, *in utero* exposure to cocaine and other illicit drugs, use of antenatal magnesium sulfate, antenatal steroid exposure, mode of delivery, 5 minute Apgar ≤ 3, respiratory distress syndrome, and total serum bilirubin concentrations prior to ABR testing.

Exposure Variable - CF Measurements

The institutional policy is to collect cord blood on all newborn infants delivered at the URMC for evaluation of infants' blood group. The cord blood collected in a red top tube is routinely stored at 4°C in a refrigerator by the institutional blood bank for two weeks. Soon after obtaining the consent for the study, the cord blood on each subject was transferred from the blood bank to the adjacent clinical chemistry laboratory for immediate measurement of serum ferritin concentrations using the chemiluminescence immunoassay method.

Outcome Variable - Auditory Brainstem Evoked Response

ABRs were recorded with a Biologic Navigator Evoked Response System with the subjects lying supine in the isolette and skin temperture > 35.5°C. Testing was performed by audiologists skilled in the administration of ABR tests to NICU infants. Electrode sites were mastoid (reference), midline on high forehead or crown of the head (active), and shoulder (ground). Electrode gel was applied to silver/silver chloride electrodes. Bilateral monaural ABR tests were performed between 24 and 48 hours after birth using 80 dB nHL broadband click stimuli with insert earphones. The clicks were presented at a repetition rate of 29.9/sec, and three runs of 2000 repetitions were recorded for each ear. The 2 most replicable runs for each ear were averaged and used for analysis. The ABRs were analyzed by the audiologists without knowledge of GA or CF concentrations. The ABR findings from the better ear in each subject were used for the final analyses of absolute latencies.

In addition, typmanometry using a 1000 Hz probe was performed in each subject to rule out middle ear disease. Transient otoacoustic emission tests were performed to rule out outer hair cell dysfunction.

Since ABR waves I, III, and V cannot be detected in all premature infants ≤ 33 weeks GA, ABR waveforms were categorized into Response Types based on response replicability and peak identification: Type 1, a waveform with normal morphology and replicable waves III and V (mature response type); Type 2, a replicable response with either a wave III or V; Type 3, a replicable response with neither a wave III or V; Type 4, a waveform with no replicable response.(19) The categories from Type 4 to Type 1 are in order from immature to mature ABR waveform. If the waveform was Type 1 or Type 2, latencies for waves I, III, & V were measured. If the Response Type was 1 in both ears, it was considered a mature ABR Response Type for that particular subject.

Statistical Analyses

Analyses were performed using SAS (version 9.1, SAS Institute Inc, Cary, NC). The subjects with latent iron deficiency and those with normal iron status were compared using 2-sample t-tests for continuous variables and the Chi-square or Fisher's exact test as appropriate for categorical variables. Repeated measure analysis using linear mixed model was carried out to test the difference in better ear absolute latencies between latent iron deficiency and normal iron status groups, with I, III, and V absolute latencies as multiple outcomes for each subject.

Variables associated with iron status or auditory maturation on bivariate analysis ($p < 0.1$) were considered potential confounders and included in regression analysis. Unstructured variance covariance matrix was specified. The significance level of the data analysis was set at 0.05.

RESULTS

A total of 153 infants, 27–33 weeks GA, were born and admitted to the NICU at URMC between July 2007 and November 2008. Of these, 13 infants were excluded (4 infants died within 24 hours after birth, 7 were unstable, 1 infant had chromosomal syndrome and 1 infant had craniofacial anomaly). Of remaining 140 infants, 108 infants had cord blood collected soon after delivery. Of these 108 infants, 80 consented and were enrolled. The mean GA of infants who did not consent was 29.2 weeks and was not different from those who consented. Thirty five (44%) infants were categorized to have *in utero* latent iron deficiency (CF concentration 11–75 ng/ml, mean 42 ng/ml, median 41ng/ml) and 45 premature infants had normal *in utero* iron statuts (CF concentration > 75 ng/ml, mean 164 ng/ml, median 118 ng/ml). Mothers of all enrolled subjects had good prenatal care and only two were diagnosed with iron deficiency anemia during pregnancy. Each subject had a hematocrit > 35 at birth and none were anemic before ABR evaluation. None of the subjects had hypoglycemia prior to ABR evaluation. None of the subjects were diagnosed with hypothyroidism during the neonatal period. The characteristics of study patients as a function of *in utero* iron status are shown in Table I. There were no significant differences between the two groups in demographic and perinatal factors except for cesarean section, maternal history of diabetes, and unconjugated hyperbilirubinemia.

Wave Latencies

None of the study subjects had an abnormal oto-acoustic emision test or tympanometry. The stratified analysis for the effect of iron status on each of the absolute latencies are provided in Table II. Infants with latent iron deficiency had significantly prolonged absolute latencies III and V (using better ear for each infant) compared with infants with normal iron status (Table II). There was a non-significant trend for absolute latency I to be prolonged in infants with latent iron deficiency compared with infants with normal iron status. By fitting linear mixed effects model with better ear absolute latencies I, III, and V as multiple responses for each subject, infants with latent iron deficiency had significantly prolonged absolute latencies I, III, and V as compared with infants with normal iron status after controlling for cesarean section, maternal diabetes, and total serum bilirubin concentration ($p = 0.01$).

ABR Response Types

Infants with normal iron status had a trend for a higher frequency of mature ABR Response Type compared with infants with latent iron deficiency as shown in Table II ($p = 0.08$). Among infants with normal iron status, 35% of infants had a complete ABR waveform (all three absolute waves present), and only 14% of infants with latent iron deficiency had a complete ABR waveform ($p = 0.2$).

DISCUSSION

Iron deficiency is the most common nutrient deficiency in the world.(24) Although ample evidence exists from animal studies regarding the role of iron for fetal and neonatal brain development, little human data exists regarding *in utero* iron status and its concomitant effect on brain development.(3–5,14) Our findings suggest that CF concentration, an index measurement for *in utero* iron status, is associated with auditory neural maturation when evaluated by ABR soon after birth in premature infants.

Progressive development is seen in the fetal auditory nervous system during the last trimester of pregnancy and iron is an essential nutrient for this critical development of the nervous system.(4,21) ABR has been used as a non-invasive tool to assess auditory neural maturation in premature infants as a function of enteral feedings, taurine supplementation, hypothyroxinemia, and antenatal steroid exposure.(18,22,25–27) By evaluating the wave latencies, which are influenced by the degree of myelination, axonal growth, dendritic growth, and synaptic function, inferences can be made about the possible effects of iron status on auditory neural maturation, a surrogate outcome for brain maturation.

Several previous observational studies in infants and older children have used ABR to evaluate the effect of iron deficiency anemia on brain development.(23,28–32) Although these studies demonstrated an association between ABR changes and iron status, they involved older infants with iron deficiency anemia which is a late manifestation of iron deficiency. Therefore, these studies also failed to answer the question whether iron deficiency without anemia causes neurological impairment. The ABR changes were irreversible despite correction of iron status and anemia with iron therapy.(28) Several studies have demonstrated that brain and other tissues are depleted long before red blood cells are depleted and, therefore, early identification and treatment of iron deficiency before anemia develops may be essential.(9,11,16)

Compared with studies in older children which evaluated specific neurodevelopmental process such as myelination using interpeak latencies, our study was aimed to evaluate auditory neural maturation. Most premature infants < 33 weeks GA do not have a complete ABR waveform with all three absolute wave latencies necessary for measuring interpeak latencies, a surrogate marker of myelination. In our study group, more infants with latent iron deficiency had immature ABR waveform compared with infants with normal iron status. Our findings strongly suggest that iron status in the absence of anemia influences auditory neural maturation at both auditory nerve (wave I latency) and brainstem level (wave III and V) and infants with latent iron deficiency have abnormal auditory neural maturation compared with infants with normal iron status.

Some of the perinatal factors such as preeclampsia may be associated with accelerated auditory neural maturation, and hyperbilirubinemia may be associated with transient ABR changes including prolongation of wave latencies.(33,34) Most studies have reported no significant changes in auditory neural maturation among small for GA infants compared with appropriate for GA infants.(35,36) Despite the fact that more infants with latent iron deficiency were born to mothers with pre-eclampsia and had lesser degree of hyperbilirubinemia, we found that absolute latencies were prolonged in infants with latent iron deficiency compared with infants with normal iron status.

There is growing evidence from observational studies that latent iron deficiency during the fetal and neonatal period may be associated with acute and long-lasting detrimental effects on neurodevelopment.(15–17) Tamura et al reported that late preterm and term infants born with CF < 76 ng/ml had poorer performance in fine motor skills and language development at 5 years of age than those with CF ≥ 76 ng/ml, (17) In another study involving term infants of diabetic mothers, infants with CF ≤ 34 ng/ml had poorer auditory recognition memory as newborns and lower psychomotor developmental scores at 1 year of age than term infants of diabetic mothers with CF > 34 ng/ml.(16) In the only study involving premature infants < 34 weeks GA, serum ferritin concentration < 75 ng/ml was associated with abnormal neurobehavioral status at 37 weeks post-menstrual age.(15) Our findings that *in utero* iron status strongly influences auditory neural maturation are consistent with the findings of Tamura et al and Sidappa et al.(16,17) Our study differs from previous studies in two ways. Our study population was different and involved more premature infants. Secondly, we measured concomitant effects of latent iron deficiency on brain maturation using ABR. Further

meaningful analysis of our ABR data using a CF < 35 ng/ml as reported by Sidappa et al was not possible as there were only 3 subjects with CF < 35 ng/ml and measurable absolute latencies in our study group.

The major strength of our study is the objective assessment of an ABR outcome after confirming absence of middle ear disease and outer hair cell dysfunction. Moreover, Response Type assignments were done by audiologists without knowledge of the infants' CF concentrations. Because our study was limited to 27 to 33 weeks GA infants, our findings may not be generalizable to premature infants > 33 weeks GA. Our findings suggest that ABRs may be a surrogate outcome marker that can be used to assess the potential effect of iron status on brain maturation during the critical period of brain development.

In summary, our findings suggest that iron status influences auditory neural maturation in premature infants. The little evidence currently available suggests that the effect of iron deficiency on neurodevelopment may be long-lasting.(16,17,37–39) Latent iron deficiency is very common among premature infants, and if the subtle neurodevelopmental changes secondary to latent iron deficiency in the neonatal period lay the foundation for abnormal long-term cognitive, motor, language, and behavioral functioning, then a large unrecognized population of premature infants could be at risk as a consequence of an easily treatable nutritional deficiency.(16,17,40,41) Therefore, there is an urgent need to determine if there is a causal relationship between latent iron deficiency and abnormal brain development. To establish a causal relationship, a well designed randomized clinical trial is warranted in high-risk premature infants using an objective test such as the ABR. A similar trial during pregnancy, although feasible, will be technically difficult to conduct without knowledge of at-risk fetuses.

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Abbreviations

GA	gestational age
ABR	auditory brainstem evoked response
NICU	neonatal intensive care unit
CF	Cord Ferritin
URMC	University of Rochester Medical Center

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Table 1

Characteristics of Study Population as a Function of *In Utero* Iron Status

	Latent Iron Deficiency Cord Ferritin 11–75 ng/ml (N = 35)	**Normal Iron Status Cord Ferritin > 75 ng/ml (N = 45)**	***P***
Birth Weight (g)*	1271 ± 386	1325 ± 371	0.5
Gestational Age (wks)*	29.1 ± 1.4	29.4 ± 2	0.3
Sex (Male/Female)#	20/15	21/24	0.35
Race (% White)#	74	62	0.25
Small for Gestational Age (%)	17	4	0.13
Pregnancy Induced Hypertension (%)	26	13	0.16
Exposure to Magnesium Sulfate (%)#	48	44	0.71
Maternal Diabetes (%)	17	0	0.01
Maternal Chorioamnionitis (%)#	0	9	0.13
In utero Exposure to Illicit Drugs (%)#	11	18	0.43
Exposure to Antenatal Steroids (%)	88	75	0.14
Rate of C-section Delivery (%)#	71	49	0.04
Apgar Score ≤ 3 at 5 minutes (%)	0	0	NS
Respiratory Distress Syndrome (%)	89	78	0.2
Total Serum Bilirubin (mg/dl)*	5.6 ± 1.4	6.2 ± 1.2	0.05

*Mean ± SD using t-test,

#proportions analyzed using Chi-square test or Fisher exact test,

**
p-value significant, NS non-significant

Table 2

Absolute Latencies and Mature ABR Response Type as a Function of *In Utero* Iron Status

	Latent Iron Deficiency Cord Ferritin 11 – 75 ng/ml (N = 35)	**Normal Iron Status Cord Ferritin > 75 ng/ml (N = 45)**	***P***
Absolute Latencies*			
Latency I (msec)	2.68 ± 0.75	2.17 ± 0.57	0.06**
Latency III (msec)	6.73 ± 0.99	6.11 ± 0.91	0.02**
Latency V (msec)	9.84 ± 1.02	9.26 ± 0.99	0.02**
Response Type			
Mature ABR Response Type (%)	34%	53%	0.08#

*Mean (SD),

**using F-test

#using Chi-square test