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Hyperbilirubinemia and Language Delay in Premature Infants

Sanjiv B Amin, MD, MS[#], **Diane Prinzing, AAS**[#], and **Gary Myers, MD**[#]
[#]Department of Pediatrics, Division of Neonatology, University of Rochester School of Medicine

Abstract

Objective—To evaluate if language delay at three years in premature infants is associated with prior exposure to hyperbilirubinemia during the first two weeks after birth.

Patients and Methods—We performed retrospective case-control study of infants admitted to the Neonatal Intensive Care Unit between January and October 2003. Inclusion criteria included a birth weight ≤ 1500 grams and follow-up to age three years. Exclusion criteria included genetic disorders and hearing loss or recurrent ear infections. Peak total serum bilirubin (TSB) during the first two weeks and duration of hyperbilirubinemia (days with TSB > 8 mg/dl) were determined. Infants with language delay and receiving speech therapy by three years were identified through developmental clinic charts and tracking program and compared to infants who had normal language development.

Results—125 infants with birth weight ≤ 1500 grams were admitted to the Neonatal Intensive Care Unit between January and October 2003. Fifteen infants died and 110 were discharged home. 102/110 (93%) of infants had follow-up to age three years. Four infants were excluded (1 genetic disorder, 3 delayed hearing loss or recurrent ear infections). 24 infants had a language delay and received speech therapy while 74 infants had normal language development. There was no significant difference in peak TSB and duration of hyperbilirubinemia between the two groups. On logistic regression, only bronchopulmonary dysplasia was associated with language delay (Adjusted odds ratio 7.3, 95% confidence interval 2.5 – 22).

Conclusions—Hyperbilirubinemia defined as peak TSB level or duration of elevated bilirubin in days is not associated with language delay in premature infants. However, this issue deserves investigation since other measures of bilirubin, such as unbound bilirubin may be associated with language delay.

Keywords

hyperbilirubinemia; premature infants; language

INTRODUCTION

Premature infants are at increased risk of developmental language disorders.(1–3) The reasons for this are not well understood, but auditory development is known to be intricately related to language development.(4–9) Auditory sensory deprivation during critical period of development has been demonstrated to lead to central auditory processing and language problems.(10–12) Studies in neonates and children have associated auditory dysfunction as evaluated by auditory brainstem evoked response with developmental language disorders. (13–15)

Corresponding Author: Sanjiv B Amin, MD, PO Box 651, 601 Elmwood Avenue, Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, NY -14642, Tel: 585-275-2972, Fax: 585-461-3614, Sanjiv_Amin@urmc.rochester.edu.

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The auditory neural system is known to be sensitive to bilirubin-induced neurotoxicity.(16) Several large observational studies have been conducted to evaluate the association between neurodevelopmental outcomes and hyperbilirubinemia in premature infants.(17–20) The only significant and consistent association demonstrated has been between hyperbilirubinemia and hearing deficits.(17, 19) These observational studies did not specifically evaluate language development in association with hyperbilirubinemia. Recently, hyperbilirubinemia has been associated with auditory dysfunction as evaluated by auditory brainstem evoked responses in premature infants.(21) Despite knowledge about the effect of hyperbilirubinemia on the auditory system and the intricate developmental relationship known to exist between auditory and language development, there is limited information available in the literature regarding the effect of indirect hyperbilirubinemia on language development in premature infants.(22) We hypothesized that premature infants with language delay identified during the first 3 years of postnatal life have a higher peak total serum bilirubin (TSB) level and/or a longer duration of hyperbilirubinemia during the first two postnatal weeks compared to premature infants with normal language development. Our objective was to determine if a language delay at age 3 years in premature infants is associated with the severity or duration of hyperbilirubinemia during the first two postnatal weeks of life.

METHODS

Study Design

A retrospective case-control study was designed to determine whether the severity or duration of hyperbilirubinemia during the first 2 weeks of postnatal life was related to a language delay at age 3 years in premature infants. We compared premature infants with a birth weight ≤ 1500 gm who received speech therapy by age 3 years with those who did not. Speech therapy was used as a surrogate measure of language delay and its absence a surrogate measure of normal language development. The study was approved by the Institutional Research Review Board.

Subject Population

All premature infants ≤ 1500 grams admitted to the Neonatal Intensive Care Unit (NICU) at the Golisano Children's Hospital at Strong between January and October 2003 and who had neurodevelopmental follow-up at age 3 years were eligible. We excluded those with a major congenital malformation, delayed hearing loss (normal newborn hearing screen but diagnosed to have hearing loss at a later period), or recurrent ear infections (>3/yr during first 3 years).

Language Evaluation and Speech Therapy

The NICU at the Golisano Children's Hospital at Strong offers a neuro-developmental clinic for high risk graduates. Families of premature infants with birth weight ≤ 1500 gm are advised on discharge to follow-up in the neuro-developmental clinic during the first few years. In the neuro-developmental clinic, the infants are evaluated by a neurologist, psychologist and a neonatologist. Infants with suspected or confirmed speech and language delay, based on the assessment by the psychologist on the speech and language domain of Bayley Infant Neurodevelopmental Screener, are referred to the Early Intervention Program for further evaluation and therapy. Infants may also be referred to the Early Intervention Program by their primary care physician. Most primary care physicians use the Denver Developmental Screening Test II in their clinic. Infants are then evaluated by the speech pathologist involved with the Early Intervention Program using one of the standardized language assessment tools approved by the New York State Early Intervention Program. The standardized tools used are either the Preschool Language Scale (fourth edition) or Parent

Receptive Expressive Emergent Language test (third edition). If an infant shows a 33% delay in speech acquisition based on this evaluation then the infant is determined to have speech and language delay and is offered speech therapy for a minimum of 6 months.

After the second year evaluation in the neuro-developmental clinic, each child is followed through the Neonatal Continuity Care Tracking Program (NCCTP) from 3 to 10 years of age. This involves sending a survey questionnaire to parents and primary care physician of each subject on developmental milestones achieved, interval medical illness, interval hospitalization, interval surgical operations, current medications, and type of therapy for any developmental issues the child is currently receiving or has received.

Study Groups

We identified infants who had follow-up data at age 3 years through the NCCTP. Among these infants, those who had received speech therapy were identified and constituted the Case group. Those infants with normal language development who did not receive speech therapy constituted the Control group.

Exposure Variables

Information on total serum bilirubin levels during the first 2 postnatal weeks for each individual subject was obtained from the Clinical Information System. TSB levels were measured using the Diazo method. Peak TSB and duration in days of total serum bilirubin > 8 mg/dl during the first 2 postnatal weeks was determined for each subject. Data on demographics and covariates were extracted from neonatal charts by investigators blinded to language outcome. Patent ductus arteriosus (PDA) was reported by the pediatric cardiologist based on echocardiography findings. Intraventricular hemorrhage (IVH) grading on head ultrasound findings was based on Papille's classification and was reported by the pediatric radiologist. Periventricular leukomalacia (PVL) was defined and reported by the pediatric radiologist based on head ultrasound findings of echo lucent cysts in the white matter. Head ultrasounds were routinely performed during the first postnatal week, at the end of second postnatal week, and at 6– 8 weeks after birth. Bronchopulmonary dysplasia (BPD) was defined based on oxygen requirement at 36 weeks post-menstrual age. Necrotizing enterocolitis (NEC) was defined based on x-ray findings of pneumatosis and/or free air in the peritoneum as reported by the pediatric radiologist. Clinical sepsis was defined as a clinical condition associated with the use of intravenous antibiotics for ≥ 5 days.

Statistical Analyses

Student's t test was used to analyze continuous variables using Stata (Stata Corporation, College Station, TX). A Chi-square or Fisher's exact test as appropriate was used to analyze nominal variables. Stratified analyses with homogeneity tests were used to evaluate for possible effect modifiers. Bivariate analyses were performed to evaluate the association between each clinical variable (covariates) and language outcome. Similarly, bivariate analyses were performed to evaluate the association between covariates and exposure variables (duration of hyperbilirubinemia and peak TSB levels). All tests were two sided and a $P < .05$ was considered statistically significant.

Covariates with a significant association ($p < 0.2$) to language outcome or exposure variables were considered as possible confounders and included in model building. Log likelihood ratio test was performed to evaluate the regression model using backward selection method. Covariates that did not make significant contribution to the model ($p < 0.2$) as evaluated by the log likelihood ratio test were removed from the model. The final model was evaluated for a fitness using Hosmer Lemeshow test. A logistic regression analysis was performed using final model to control for potential confounding factors.

RESULTS

A total of 125 infants with birth weight ≤ 1500 gm were admitted to the NICU of Golisano Children's Hospital from January to October, 2003. Among them 15 infants died and 110 infants were discharged home. There were 102 (93%) infants who had follow-up until age 3 years. Four infants were excluded (1 genetic disorder, 3 with delayed hearing loss or recurrent ear infections). Of the remaining 98 infants, 74 identified as having normal language were compared to 24 infants with a language delay.

The demographics of the study subjects are shown in Table 1. There was no significant difference in gestational age, birth weight, gender, race, maternal education, *in-utero* exposure to illicit drugs, rate of cesarian section delivery, and 5 minute Apgar < 3 between infants in the two groups. The clinical characteristics of study subjects are shown in Table 2. There were no significant differences in the occurrence of RDS, PDA, severe IVH, PVL, type of enteral feeding and clinical sepsis between infants with normal language development and infants with language delay. There was a significant association between BPD at 36 weeks postmenstrual age and language delay and there was a trend for significant association between NEC and language delay. There was no significant difference in peak TSB or duration of hyperbilirubinemia between infants with normal language development and infants with language delay (Table 2).

Stratified analyses with homogeneity tests revealed no effect modifiers for the association between hyperbilirubinemia and language delay. Gestational age, birth weight, BPD, PDA, NEC, and clinical sepsis were identified as possible confounders for the evaluation of any association between hyperbilirubinemia and language delay and were included in the full regression model. The final regression model was determined using backward selection method and log likelihood ratio test. The final regression model for the evaluation of an association between hyperbilirubinemia and language development included BPD. The Hosmer Lemeshow test suggested that there was no difference in the expected frequencies and observed frequencies and that the final regression model was a good fit ($p = 0.60$). BPD was associated with language delay in premature infants (Adjusted odds ratio 7.3, 95% confidence interval (CI) 2.5 – 22). Neither peak TSB (Adjusted odds ratio 0.96, 95% CI 0.7 – 1.3) nor duration of hyperbilirubinemia (Adjusted odds ratio 1.03, 95% CI 0.8 – 1.3) was associated with language delay in premature infants with birth weight ≤ 1500 grams after controlling for confounders.

DISCUSSION

We found no relationship between peak TSB or total days of bilirubin above 8mg/dl during the first two weeks of life and language development defined as receiving speech therapy during the first 3 years of life. These findings do not support the hypothesis that there is a relationship between the severity or duration of neonatal hyperbilirubinemia and language development in premature infants with birth weight ≤ 1500 grams. We believe this is the first study to evaluate the role of severity and duration of hyperbilirubinemia on language development in premature infants.

Language delay is one of the most common developmental problems among premature infants, but its causes have not been determined.(1–3, 23, 24) Hearing is essential to language development and there is evidence that peripheral auditory dysfunction or auditory sensory deprivation during the critical period of development may affect central auditory function and later language development. (10–12, 25) Children with hearing loss and/or auditory neuropathy may demonstrate language problems depending on the timing, degree, and duration of associated auditory dysfunction or auditory sensory deprivation.(26–29)

Auditory neuropathy is characterized by normal outer hair cell function but abnormal auditory brainstem evoked responses. Earlier identification and management of these hearing problems has been shown to improve auditory processing and language development supporting the fact that these hearing disorders affect language development. (26, 30, 31)

The auditory system is thought to be most sensitive neural system to bilirubin-induced toxicity.(16, 32) Previous studies have associated hyperbilirubinemia with sensori-neural hearing loss and auditory neuropathy in neonates.(16, 17, 19, 33) Several studies have also reported reversible auditory dysfunction at the peripheral and brainstem level secondary to indirect hyperbilirubinemia, a condition extremely common during the first postnatal week in neonates.(16, 21, 34, 35) Bilirubin-induced auditory toxicity may depend on the degree and duration of indirect hyperbilirubinemia.(16, 35–37) The corollary of this evidence is that there exists a possibility that indirect hyperbilirubinemia in neonates, depending on the duration and severity of hyperbilirubinemia, may affect later language development through its effect on the auditory nervous system.

Premature infants are at higher risk of bilirubin-induced neurotoxicity than term infants.(16) Moderate hyperbilirubinemia has been shown to cause auditory dysfunction in premature infants. (16, 21) The consequences of these auditory changes on later development in premature infants are not known. There is some evidence that suggests that auditory dysfunction may be associated with later language development.(13–15) Despite supporting evidence and strong biological plausibility, the lack of association between hyperbilirubinemia and language development is intriguing and perplexing. One plausible explanation for this lack of association can be based on the free (or unbound) bilirubin theory. Current literature suggests that the unbound bilirubin level might be a better predictor than TSB of acoustic delay in nervous system.(16, 21, 38) We have previously shown that auditory changes as evaluated by auditory brainstem evoked response are more associated with unbound bilirubin than TSB. (21)

Our findings of no significant association between hyperbilirubinemia and language development are consistent with the findings reported by Ogun B et al.(22) They also reported that there was no association between severe hyperbilirubinemia and language outcomes.(22) However, our study differs from theirs. Their study involved term infants with severe hyperbilirubinemia while we studied premature infants with any degree of hyperbilirubinemia. We also evaluated the role of duration of hyperbilirubinemia. The little available data suggest that duration of hyperbilirubinemia may also be a determining factor for bilirubin-induced auditory dysfunction.(36, 37) However, when duration of hyperbilirubinemia was defined as the number of days with TSB > 8 mg/dl during the first two weeks of life, it was not associated with language delay.

Our findings of 25% incidence of language delay among premature infants with birth weight ≤ 1500 grams are consistent with the reported incidence of language delay in the literature. (2, 39) Our finding of BPD as a risk factor for language delay is also consistent with other reports.(40) BPD has also been associated with auditory dysfunction in premature infants. (41)

The major limitation of our study is its retrospective nature and associated information bias. We used information provided by the primary care physician and or the family along with medical information available from the developmental clinic charts to categorize the outcomes. Secondly, there were different standardized language evaluation tools used by the speech pathologists to determine which children needed speech therapy. We were not able to specify the characteristics of the children’s speech and language delay, specifically the

receptive and expressive components. We may have used an inadequate measure of bilirubin exposure since more recent evidence favors the use of unbound bilirubin as a biochemical measure.(21, 38, 42, 43)

The study also has several strengths. There was an excellent follow-up rate of 93%. The incidence of language delay in our cohort was similar to that reported in the literature. We found the same association with BPD as reported in the literature. In summary, we found no association between peak TSB or total duration of elevated bilirubin in premature infants and their language development. Despite these findings, we believe the association of unbound bilirubin with language delay deserves thorough investigation.

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Abbreviations

IVH	Intraventricular Hemorrhage
PVL	Periventricular Leukomalacia
NEC	Necrotizing Enterocolitis
PDA	Patent Ductus Arteriosus
TSB	Total Serum Bilirubin
NCCTP	Neonatal Continuity Care Tracking Program
BPD	Bronchopulmonary dysplasia
RDS	Respiratory Distress Syndrome
SD	Standard Deviation
CI	Confidence Interval
NICU	Neonatal Intensive Care Unit

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Table 1

Demographic Characteristics of Study Population

	Normal Language (N =74)	Language Delay (N = 24)	*P***
Gestational age (weeks)*	29.4 ± 2.2	28.4 ± 2.5	0.08
Birth weight (grams)*	1132 ± 219	1022 ± 283	0.09
Small for gestational age (%)	31	25	0.6
Gender (Male/Female)	38/36	15/9	0.3
Race (% White)	61	66	0.8
Maternal education (%) ≥ college	67	69	0.9
In-utero exposure to illicit drugs (%)	7	8	0.8
Antenatal steroid exposure (%)	88	87	0.9
Mode of delivery (% C-section)	63	50	0.21
Apgar score < 3 @ 5 minutes (%)	5	13	0.21

* Mean ± SD;

** Mean ± SD analyzed using t-test and proportions analyzed using Chi-square test

Table 2

Clinical Characteristics of Study Population

	Normal Language (N =74)	Language Delay (N = 24)	*P***
Respiratory distress syndrome (%)	90	91	0.9
Patent ductus arteriosus (%)	15	29	0.1
Grade III/IV intraventricular hemorrhage (%)	4	0	0.6
Periventricular leukomalacia (%)	2	0	1.0
Bronchopulmonary dysplasia @ 36 weeks (%)	13	54	0.001
Breast milk feeding during NICU stay (%)	44	35	0.4
Necrotizing enterocolitis with pneumatosis or perforation (%)	4	17	0.05
Clinical sepsis (%)	35	52	0.1
Peak TSB during first 2 weeks (mg/dl)*	9.9 ± 1.8	9.4 ± 2.1	0.3
Days with TSB > 8mg/dl during first 2 weeks* (duration of hyperbilirubinemia)	3 ± 2.7	2.7 ± 2.5	0.6

* Mean ± SD;

** Mean ± SD analyzed using t-test and proportions analyzed using Chi-square test; TSB denotes total serum bilirubin; NICU denotes Neonatal Intensive Care Unit