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Auditory Neuropathy Spectrum Disorder in Late Preterm and Term Infants with Severe Jaundice

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Abstract

Objective—To evaluate if severe jaundice is associated with acute auditory neuropathy spectrum disorder in otherwise healthy late preterm and term neonates.

Methods—In a prospective observational study, all neonates who were admitted with severe jaundice at which exchange transfusion may be indicated as per American Academy of Pediatrics guidelines had comprehensive auditory evaluation performed before discharge to home. Neonates with infection, perinatal asphyxia, chromosomal disorders, craniofacial malformations, or family history of childhood hearing loss were excluded. Comprehensive auditory evaluations (tympanometry, oto-acoustic emission tests, and auditory brainstem evoked responses) were performed by an audiologist unaware of the severity of jaundice. Total serum bilirubin and serum albumin were measured at the institutional chemistry laboratory using the Diazo and Bromocresol purple method, respectively.

Results—A total of 13 neonates with total serum bilirubin concentration at which exchange transfusion is indicated as per American Academy of Pediatrics were admitted to the Neonatal Intensive Care Unit over 3 month period. Six out of 13 neonates (46%) had audiological findings of acute auditory neuropathy spectrum disorder. There was no significant difference in gestational age, birth weight, hemolysis, serum albumin concentration, peak total serum bilirubin concentrations, and peak bilirubin:albumin molar ratio between six neonates who developed acute auditory neuropathy and seven neonates who had normal audiological findings. Only two out of six infants with auditory neuropathy spectrum disorder had clinical signs and symptoms of acute bilirubin encephalopathy.

Conclusions—Our findings strongly suggest that auditory neuropathy spectrum disorder is a common manifestation of acute bilirubin-induced neurotoxicity in late preterm and term infants with severe jaundice. Our findings also suggest that comprehensive auditory evaluations should be routinely performed in neonates with severe jaundice irrespective of the presence of clinical findings of acute bilirubin encephalopathy.

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Keywords

Acute bilirubin encephalopathy; auditory brainstem evoked response; exchange transfusion; oto-acoustic emission test; bilirubin:albumin molar ratio

INTRODUCTION

In most developed countries chronic post-kernicteric encephalopathy, a late sequela of severe neonatal unconjugated hyperbilirubinemia (jaundice), is extremely uncommon. [1,2] However, in developing countries chronic post-kernicteric encephalopathy is still commonly seen. [3–5] Chronic post-kernicteric encephalopathy, characterized by choreoathetoid cerebral palsy, auditory disorders, gaze paresis, and enamel hypoplasia, is a life-long debilitating disorder; therefore, early identification of at-risk infants during the neonatal period is paramount to improve long-term neurological outcomes. Total serum bilirubin concentration, the most commonly used biochemical measurement for evaluation and management, is a poor predictor of chronic post-kernicteric encephalopathy. Similarly, although clinical manifestation of acute bilirubin encephalopathy at the time of neonatal jaundice increases the likelihood of later chronic post-kernicteric encephalopathy, the signs and symptoms of acute bilirubin encephalopathy are non-specific and may be absent in neonates who later develop chronic post-kernicteric encephalopathy. [6]

Emerging evidence suggests that the auditory nervous system is the most sensitive nervous system to overt bilirubin toxicity and auditory evaluation may improve detection of bilirubin-induced neurotoxicity in neonates.[7] Although sensorineural hearing loss has been widely described as a characteristic feature of chronic post-kernicteric encephalopathy, more recently auditory dys-synchrony (auditory neuropathy spectrum disorder), an auditory disorder characterized by normal otoacoustic emission test (OAE) but abnormal or absent auditory brainstem evoked response (ABR), has been described in early childhood in association with prior history of neonatal jaundice.[7–20] The neurological findings of choreo-athetoid cerebral palsy are not usually seen until beyond infancy and the diagnosis of sensori-neural hearing loss is usually not confirmed until several months after severe jaundice. However, compared to these later manifestations of bilirubin-induced neurotoxicity, auditory neuropathy spectrum disorder can be evaluated and diagnosed at the time of neonatal jaundice. To date, most published reports of auditory neuropathy spectrum disorder have been retrospective [8–17], with very few reports involving prospective comprehensive auditory evaluations for auditory neuropathy spectrum disorder following severe jaundice in neonates.[18–20] Of the few prospective reports, only one involved prospective evaluation for auditory neuropathy spectrum disorder using diagnostic ABR at the time of unconjugated hyperbilirubinemia in otherwise normal neonates.[20] However, Ackman et al. excluded infants with severe jaundice secondary to hemolysis and failed to evaluate infants for middle ear disease that can affect ABR findings.[20] Because of limited information regarding acute auditory neuropathy spectrum disorder secondary to severe jaundice, we conducted a pilot observational study to evaluate if severe jaundice, irrespective of the cause of jaundice, is associated with acute auditory neuropathy spectrum disorder in late preterm and term neonates without any co-morbid medical conditions and middle ear disease. The study was approved by the institutional ethics committee.

METHODS

All neonates admitted to the Neonatal Intensive Care Unit (NICU) at Sir Ganga Ram Hospital in India over three months period in 2009 with severe jaundice (a total serum bilirubin at which exchange transfusion may be indicated as per American Academy of Pediatrics [AAP]

guidelines) underwent comprehensive auditory evaluation for auditory neuropathy spectrum disorder as recommended by the Joint Committee on Infant Hearing (JCIH).[21] Auditory evaluation was performed after resolution of jaundice but before discharge from the hospital. Neonates with family history of hearing loss since childhood, infection, perinatal asphyxia (Apgar score < 3 at 5 minutes), chromosomal disorders, or cranio-facial malformations were excluded. Total serum bilirubin concentrations on each neonate were measured as clinically indicated at the discretion of the attending neonatologist. Total serum bilirubin concentrations were measured in the institutional chemistry laboratory using the Diazo method. Serum albumin concentration was measured in each individual subject on admission to the NICU as recommended by the AAP for consideration of exchange transfusion.[22] Serum albumin concentrations were measured in the institutional chemistry laboratory using the Bromocresol purple method. The peak total serum bilirubin concentration and peak bilirubin:albumin molar ratio were the exposure variables of interest. The peak bilirubin:albumin molar ratio was calculated for each subject using the peak total serum bilirubin concentration and serum albumin concentration. All subjects were evaluated by the physician for clinical signs and symptoms of acute bilirubin encephalopathy on admission to the NICU as recommended by the AAP for consideration of immediate exchange transfusion.[22] OAE and ABR were performed in each subject by a trained audiologist. OAE was administered with an EchoChek transient OAE (Otodynamics, London, England) using an 80 decibel click stimulus. Normal OAE was defined as a replicable response (3 decibel Signal to Noise ratio) in the three highest frequency bands (2000, 3000 and 4000 Hz). ABR tests were recorded with a Biologic Navigator Evoked Response System (Bio-logic, Mundelein, IL) using alternating broadband click stimuli presented separately to each ear with a hand-held TDH -39 earphones. The clicks were presented at a repetition rate of 29.9/sec. with the subjects lying supine in the crib and skin temperture > 35.5°C. Tympanometry was performed in each ear to exclude middle ear disease on all infants. Auditory findings were evaluated by an audiologist without knowledge of medical histories. Neonates with normal OAE and abnormal or absent ABR at 80 db were considered to have auditory neuropathy spectrum disorder.

Statistical analyses were performed using Stata 10 (Stata Corporation, College Station, TX). Continuous variables were analyzed using student t-test if normally distributed otherwise Mann-Whitney test was used to analyze continuous variables between two groups. Categorical variables were analyzed using Fisher exact test. Logistic regression analyses were performed to calculate the Odds ratio with 95% confidence interval for the association of peak total serum bilirubin and peak bilirubin:albumin molar ratio with auditory neuropathy spectrum disorder.

RESULTS

A total of 13 neonates with severe jaundice within 12 days after birth were admitted to the NICU and had comprehensive auditory evaluations for auditory neuropathy spectrum disorder before discharge to home. All neonates were delivered in the hospital. None of the neonates who were evaluated for auditory neuropathy spectrum disorder had co-morbid medical condition, including infection and perinatal asphyxia. None of the neonates met exclusion criteria. All neonates were breast fed. All neonates had normal OAE and tympanometry in both ears. Of these 13 neonates, six were diagnosed with auditory neuropathy spectrum disorder. Five out of six neonates with acute auditory neuropathy spectrum disorder had abnormal ABR findings in both ears. The ABR findings of right ears on these six neonates with auditory neuropathy spectrum disorder are shown in Figure 1.

There was no significant difference in gestational age and birth weight between six neonates who developed acute auditory neuropathy spectrum disorder and seven neonates who did not develop acute auditory neuropathy spectrum disorder. (Table 1) Similarly, there was no significant difference in the mean peak total serum bilirubin concentrations and the mean peak

bilirubin:albumin molar ratio between neonates who developed acute auditory neuropathy spectrum disorder and neonates who had normal auditory findings (Table 1). The proportion of neonates with hemolysis was not significantly different between the group with auditory neuropathy spectrum disorder and the group with normal auditory findings. The specific laboratory findings for the six neonates with auditory neuropathy spectrum disorder are shown in Table 2. Two neonates had laboratory findings characteristic of hemolysis. Two out of six neonates with acute auditory neuropathy spectrum disorder had clinical findings (opisthotonus and retrocollis) of acute bilirubin encephalopathy while none of the neonates with normal auditory findings had clinical findings of acute bilirubin encephalopathy.

The peak total serum bilirubin was not associated with auditory neuropathy spectrum disorder (odds ratio 1.18, 95% CI 0.91– 1.52). Similarly, peak bilirubin:albumin molar ratio was not associated with auditory neuropathy spectrum disorder (odds ratio 144, 95% CI 0.3– 628).

DISCUSSION

Auditory Neuropathy Spectrum Disorder or auditory dsy-synchrony, first described in 1996, is characterized by an absent or poorly defined ABR with preserved OAE and/or preserved cochlear microphonics. [23–25] In most cases of auditory neuropathy, ABRs performed at 80 db are usually limited to early/fast waves (cochlear microphonics) that exhibit fixed-latency function and complete phase reversal between rarefaction and condensation stimuli.[26] In some instances of auditory neuropathy spectrum disorder, the ABR may show a wave V, but with decreased amplitude and increased latency.[23,27] In our study, six out of 13 neonates who were evaluated had auditory findings characteristic of auditory neuropathy spectrum disorder, specifically absent or abnormal ABR but normal OAE and/or preserved cochlear microphonics.

Although auditory neuropathy spectrum disorder has been related to various etiological factors in infants and children,[28] several recent reports suggest that neonatal jaundice may be one of the most common causes of auditory neuropathy spectrum disorder among late preterm and term neonates. [7–20] However, most published reports of auditory neuropathy spectrum disorder associated with neonatal jaundice were either retrospective; [8–17] or, if prospective, involved neonates with other co-morbid conditions, [18] or had auditory evaluation for auditory neuropathy spectrum disorder performed several months after severe jaundice [19]. Because auditory neuropathy spectrum disorder has also been described secondary to other co-morbid conditions that are common during the neonatal and post-neonatal period, prospective evaluations for auditory neuropathy spectrum disorder at the time of neonatal jaundice in otherwise normal neonates is necessary to establish an association between neonatal jaundice and auditory neuropathy spectrum disorder.[16,23,28] Our prospective auditory evaluation during severe neonatal jaundice in infants without the presence of other co-morbid conditions strongly suggests that severe neonatal jaundice may be associated with acute auditory neuropathy spectrum disorder and that this may be a common manifestation of acute bilirubin-induced neurotoxicity in neonates. Our findings of high incidence are in agreement with the findings of Akman et al. who in a prospective observational study reported similar high incidence with 7 out of 19 infants with severe jaundice had auditory findings of auditory neuropathy spectrum disorder.[20] However, our study differs from Akman et al. in several respects including study population, evaluation of jaundice in age in hours as recommended by the AAP [22], using total serum bilirubin concentration at which exchange transfusion is indicated for comprehensive auditory evaluation as recommended by JCIH [21], measurement of bilirubin:albumin molar ratio [22], and evaluation for middle ear disease using tympanometry. Akman et al. included neonates with total serum bilirubin concentration > 20 mg/dl, excluded infants with hemolytic jaundice, did not evaluate bilirubin:albumin molar ratio, and failed to evaluate middle ear disease that can be associated with abnormal ABR.

[20] Although hemolysis is considered to be a significant risk factor for bilirubin-induced neurotoxicity, we found no significant difference in the proportion of neonates with hemolytic jaundice between neonates who developed auditory neuropathy spectrum disorder and neonates who had normal auditory evaluation.[22]

There is growing evidence that suggests that auditory nervous system is the most sensitive nervous system to overt bilirubin toxicity in neonates.[7] Our findings also suggest that auditory neuropathy spectrum disorder may be seen in the absence of clinical manifestations of acute bilirubin encephalopathy. Four out of six infants with auditory neuropathy spectrum disorder had no clinical signs of acute bilirubin encephalopathy. Our findings are consistent with the findings of US Kernicterus registry that also reported that clinical signs of acute bilrubin encephalopathy may be absent in neonates who later develops chronic-post kernicteric encephalopathy.[6] Therefore, evaluation for auditory neuropathy spectrum disorder may be necessary in neonates admitted with severe jaundice even in the absence of clinical manifestations of acute bilirubin encephalopathy for evaluation of bilirubin-induced neurotoxicity. Although the JCIH recommends auditory evaluation for infants who have total serum bilirubin concentrations that meet exchange transfusion criteria, [21] the AAP criteria for exchange transfusion using age-specific total serum bilirubin concentration is not evidence based.[22] Moreover, several studies have shown that total serum bilirubin is a poor predictor of bilirubin-induced neurotoxicity, including for long-term neurological outcomes.[29–31] In our study, one of the infants barely met the exchange transfusion criteria but still developed auditory neuropathy spectrum disorder. This raises questions regarding appropriateness of JCIH recommendation for using total serum bilirubin concentration that meets exchange transfusion as an indication for performing comprehensive auditory evaluations.[21] It is possible that infants with total serum bilirubin concentrations lower than the total serum bilirubin concentration at which exchange transfusion is indicated may develop auditory neuropathy spectrum disorder. Until further evidence of a safe total serum bilirubin level for bilirubin-induced auditory toxicity, it may be more prudent to use a total serum bilirubin concentration of ≥20 mg/dl, and/or total serum bilirubin concentration at which exchange transfusion may be indicated as a cut-off for comprehensive auditory evaluation.

Although our findings of no significant difference in total serum bilirubin and bilirubin:albumin molar ratio between those who developed auditory neuropathy spectrum disorder and those who had normal auditory evaluation suggests that these biochemical measures may have limited predictive value for identifying neonates at-risk for acute auditory neuropathy spectrum disorder, our study was not adequately powered to evaluate the usefulness of these biochemical measures. The pathogenesis of bilirubin-induced neurotoxicity is very complex. According to current theory, free or unbound bilirubin crosses blood brain barrier and causes neurotoxicity. [32] Emerging evidence from several recent studies support the theory that unbound bilirubin (free bilirubin) may be a better predictor of bilirubin-induced neurotoxicity than total serum bilirubin and bilirubin:albumin molar ratio. [7,30] However, usefulness of unbound bilirubin has not been systematically evaluated using auditory neuropathy spectrum disorder and/or sensori-neural hearing loss as an outcome in premature and term neonates. Until further confirmation of the usefulness of unbound bilirubin measurement from future clinical studies and availability of technology for unbound bilirubin measurement, total serum bilirubin and bilirubin:albumin molar ratio should be used for the management of severe jaundice as recommended by the AAP.[22] In term infants with hyperbilirubinemia, the bilirubin:albumin molar ratio has been shown to be more predictive of bilirubin-induced neurotoxicity than the total serum bilirubin, and the AAP recommends routine measurement of albumin for infants admitted with severe jaundice.[7,22,31]

Our finding of a high incidence of acute auditory neuropathy spectrum disorder among neonates with severe jaundice is of great public health significance considering the incidence

of severe jaundice at near epidemic proportions among some developing countries.[3–5,33] If our findings are true, a significant proportion of neonates with severe jaundice may be suffering from a preventable auditory disorder in developing countries. Identification of children with auditory neuropathy spectrum disorder is important because their clinical characteristics and treatment differ from other cases of hearing loss in children.[24] A typical child with auditory neuropathy spectrum disorder presents with difficulty understanding speech that is out of proportion to the audiometric threshold impairment. These children with auditory disorders may also be at increased risk for abnormal language development. [34] Therefore, the overall economic cost to the society in developing countries could be substantial from jaundice-induced auditory toxicity. [35] Since the use of hearing screening tests such as OAE or automated-ABR, alone has limitations in identifying cases of auditory neuropathy spectrum disorder [23,24], all late preterm and term infants with severe hyperbilirubinemia (total serum bilirubin $\geq$ 20 mg/dl) or total serum bilirubin concentration at which exchange transfusion is indicated should have comprehensive auditory evaluation performed before discharge from the hospital to identify infants with auditory neuropathy spectrum disorder. Early identification and intervention of infants with auditory neuropathy spectrum disorder may improve the long-term neuro-developmental outcome of these infants. Our findings also has research implication, specifically auditory neuropathy spectrum disorder may be a useful and more sensitive outcome measure to evaluate usefulness of bilirubin-albumin binding variables in neonates.[7] Future studies are urgently needed to evaluate the incidence, natural course, and consequences of jaundice-associated acute auditory neuropathy spectrum disorder. Future studies are also warranted to evaluate the prognostic significance of identifying infants with acute auditory neuropathy spectrum disorder, specifically whether it will improve identification of infants at-risk for chronic post-kernicteric encephalopathy.

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Abbreviations

NICU	neonatal intensive care unit
ABR	auditory brainstem evoked response
OAE	oto-acoustic emission test
JCIH	Joint Committee on Infant Hearing
AAP	American Academy of Pediatrics

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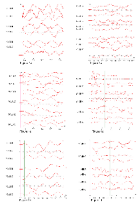

Figure 1.
Auditory brainstem evoked responses in right ears of individual subjects (1a to1f). Auditory brainstem evoked responses performed at various intensities and with alternate polarity. R denotes rarefaction and C denotes condensation.

Table 1

Demographic Features and Peak Bilirubin Binding Variables as a Function of Auditory Neuropathy Spectrum Disorder

	Normal Auditory Evaluation (n = 7)	Auditory Neuropathy Spectrum Disorder (n = 6)	*P* -value
Gestational Age (weeks)	37 ± 2.6	37.5 ± 1.4	0.38*
Birth weight (grams)	2863 ± 654	2685 ± 453	0.43*
Male/Female	6/0	4/2	0.56#
Hemolytic jaundice (%)	29	33	0.83#
Peak Total Serum Bilirubin	23 ± 7.3	27.9 ± 2.4	0.17*
Peak Bilirubin: Albumin Molar Ratio	0.9 ± 0.27	1.13 ± 0.14	0.13*

*Rank sum test;

#Fisher Exact Test

Table 2

Laboratory Findings of Neonates with Auditory Neuropathy Spectrum Disorder

Case #	Hemoglobin g/dL	Reticulocyte (%)	Coombs Test	G6PD Test	* Peak TSB (mg/dL)	Albumin (g/dL)	Bilirubin:Albumin Molar Ratio
1	15.6	2.1	negative	normal	23.4	2.9	0.91
2	15.1	1.5	negative	normal	29.9	2.8	1.2
3	14.9	8.4	positive	normal	29	2.9	1.13
4	10.4	4.4	negative	abnormal	27.6	2.7	1.15
5	15	2.6	negative	normal	27.6	2.9	1.07
6	14.3	2.2	negative	normal	30	2.5	1.35

* TSB denotes total serum bilirubin