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Unbound Unconjugated Hyperbilirubinemia is Associated with Central Apnea in Premature Infants

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Abstract

Objective—To evaluate if jaundice, indexed by unbound bilirubin (UB), is associated with central apnea in premature infants.

Study design—A prospective observational study was performed with 27–33 weeks gestational age infants who were not requiring either mechanical ventilation or non-invasive ventilation with continuous positive airway pressure beyond 24 hours after birth. Infants with congenital infections, chromosomal disorders, cranio-facial anomalies, and/or family history of hearing loss were excluded. Total serum bilirubin and UB were measured twice daily during the first postnatal week and then when clinically indicated. Central apnea was evaluated by visual inspection of continuous electronic cardio-respiratory recordings until two weeks of age.

Results—100 infants were sub-divided into two groups using the median peak UB level: High UB group (> median) and Low UB group (< median). The High UB group had an increased frequency of apnea events during the first two weeks compared to infants with the Low UB group. After controlling for confounders, the High UB group had more apnea events during the first two postnatal weeks compared to the Low UB group (Incidence Rate Ratio: 1.9, 95% CI: 1.2–3.2).

Conclusions—Our findings suggest that jaundice, as indexed by UB, is associated with central apnea in premature infants.

Keywords

bradycardia; desaturation; unbound bilirubin

Central apnea, usually defined as cessation of breathing for ≥ 20 seconds as evaluated by impedance technology, is extremely common among premature infants born ≤ 33 weeks

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gestational age.(1, 2) Central apnea in premature infants is a manifestation of developmental immaturity of respiratory control mediated by the brainstem.(1–3) Therefore, clinical conditions that may be associated with brainstem dysfunction may be associated with central apnea. Unconjugated hyperbilirubinemia, a ubiquitous medical problem among premature infants during the first postnatal week, has been associated with brainstem dysfunction, as evaluated by serial auditory brainstem evoked responses (ABR) in premature infants.(4, 5) This bilirubin-induced brainstem dysfunction (transient bilirubin encephalopathy) was predicted by unbound bilirubin (UB) and not by total serum bilirubin (TSB).(5) As UB increases and transient brainstem dysfunction occurs, the likelihood of central apnea may also increase in this population of premature infants with immature respiratory control.

We previously reported in a retrospective study that premature infants with transient bilirubin induced brainstem dysfunction as evaluated by ABR had more concurrent apnea and bradycardia and required more prolonged respiratory support and methylxanthine therapy.(6) Furthermore, apnea was more closely associated with serum UB level than TSB. (6) However, apnea evaluation was based on nursing documentation of apnea. However, nursing documentation of apnea may be inaccurate when compared with event monitoring using event-recorder monitors that allows for visual inspection and analysis of electronic cardio-respiratory waveform.(7) We, therefore, performed a prospective study to determine if unconjugated hyperbilirubinemia, as indexed by UB, is associated with central apnea during the first two postnatal weeks in premature infants.

METHODS

A prospective observational study was performed to evaluate the association between unconjugated hyperbilirubinemia and central apnea. All infants born between 27 – 33 weeks' gestational age (GA) at the University of Rochester Medical Center and admitted to the Neonatal Intensive Care Unit (NICU) were eligible. Infants that were not requiring either mechanical ventilation or non-invasive ventilation with continuous positive airway pressure (CPAP) beyond 24 hours of age were eligible. The exclusion criteria were: (1) infants with toxoplasmosis, rubella, cytomegalovirus, syphilis, herpes, or human immunodeficiency viral infection; (2) infants with craniofacial malformations; (3) infants with chromosomal abnormalities; and (4) infants with a family history of congenital hearing loss. The study was approved by the local Institutional Research Board and parental consent was obtained for each subject.

A central apnea was defined as one for which visual inspection and analysis of continuous electronic cardio-respiratory and oxygenation waveform on the central monitor verified a respiratory pause ≥ 20 sec or a respiratory pause of 15 sec or greater if associated with a heart rate < 80/minute or oxygen saturation < 85%. Bradycardia was defined as a heart rate < 80/minute. Desaturation was defined as oxygen saturation < 85%. A significant bradycardia was defined as bradycardia associated with desaturation within 2 minutesof bradycardia.

As part of the standard of care, all premature infants admitted to the NICU are monitored for central apnea using a cardio-respiratory event-recording capable monitor at the bedside.(8)

All infants received methylxanthine therapy for central apnea at the discretion of the attending neonatologist.

All infants were also monitored using central monitors (Clinical Information Center, General Electric Company). The central monitor uses impedance technology, but records events in real time and stores data in memory for 72 hours. The bedside cardio-respiratory monitors and central monitors were programmed to record all respiratory pauses lasting ≥ 15 sec, heart rate declines to ≤ 100 beats per minute, and oxygen saturations < 85%. Central monitors provide objective assessment of true central apnea by visual inspection of electronic cardio-respiratory waveforms.(7) Each of the apnea events recorded on bedside cardio-respiratory monitors on each day during the first two weeks were visually inspected and analyzed by an investigator using the continuous electronic waveform tracings on central monitors within 2 minutes of the documented event on the bedside monitor. In addition, on each day during the first two weeks, events recorded on the central monitor were visually inspected and analyzed by an investigator using the continuous electronic waveform. All premature infants were evaluated for the number of central apnea and significant bradycardia on each day during the first two postnatal weeks by an investigator unaware of bilirubin-biochemical measures including UB concentration.

For each subject, blood samples were drawn twice daily at least 8 hours apart during the first postnatal week and thereafter as clinically indicated to measure TSB (mg/dL, multiply by 17.1 to convert to μmol/L). The same aliquot of blood was also used to measure UB (μg/dL, multiple by 17.1 to convert to nmol/L). The blood samples were collected in special amber colored serum separator tubes to protect them from light exposure. Each sample was centrifuged and analyzed immediately for UB or stored in a −80° C freezer for not more than a month before analysis of UB.(9) TSB was measured in the chemistry laboratory using colorimetric method. UB was measured by the validated modified peroxidase method at two enzyme concentrations of pre-calibrated peroxidase (supplied by Arrows Co, Ltd; Osaka Japan) using the Food and Drug Administration approved Arrows UB analyzer UA-1 (Arrows Co, Ltd; Osaka Japan).(10) The peroxidase was standardized using bilirubin standard (0.67 mg/mL) and albumin free solution (i.e. total bilirubin = UB) to determine the first order rate constant (Kp) for the oxidation reaction. The Kp of the peroxidase enzyme, supplied by the Arrows Company, was 1 per minute. The peak TSB and peak UB were determined for each subject. Infants were sub-divided into two groups using the median peak UB level: High UB group (> median) and Low UB group (< median).

Data on demographic and perinatal factors such as pregnancy induced hypertension, maternal magnesium sulfate exposure, antenatal steroid exposure, chorioamnionitis, mode of delivery, and asphyxia (Apgar score < 3 at 5 minutes) were prospectively collected on each individual subject. In addition, information on neonatal factors such as respiratory distress syndrome (RDS), severe intraventricular hemorrhage (≥ grade II IVH), sepsis (culture proven or clinical sepsis requiring intravenous antibiotic therapy for more than 3 days), and patent ductus arteriosus (PDA) were prospectively recorded for each individual subject during the first two weeks after birth. IVH was defined based on head ultrasonography and graded based on Papile's classification. PDA was defined based on echocardiography.

An approximate sample size was determined for the number of infants to be studied based on the findings of our previous study.(7) Assuming the baseline rate of apnea during the first week to be 4.3, a sample size of 100 (categorized into High and Low UB groups using the median peak UB as a cut-off) will achieve 80% power to detect a rate ratio of 1.3 (30% higher in High UB group *vs*. Low UB group) in the frequency of apnea during the first week at a two sided significance level of 5%.(11

Statistical Analyses

The analyses were performed using version 9.3 of the SAS System for Windows (SAS institute Inc., Cary, NC, USA). Student t-tests were used to compare continuous variables between groups if the data were approximately normally distributed; otherwise, the Wilcoxon-Ranked Sum test was used. Chi-square or Fisher exact test was used to compare categorical variables. All tests were two sided and a $P < .05$ was considered statistically significant.

Due to the highly skewed and over-dispersed data structure of the outcome variables, a negative binomial regression model was used to evaluate the association between UB and frequency of central apneas during the first two postnatal weeks with the UB group as an independent variable. Variables identified to be associated with apnea and or the UB group ($p < 0.15$) were considered potential confounders. Robust sandwich standard errors were estimated empirically using a Generalized Estimating Equation. This approach forgoes the distribution assumption, providing consistent and robust estimates by specifying marginal mean effects on the outcome variable. Model selection was performed using quasi likelihood information criterion, with lowest quasi likelihood information criterion values preferred for the final model. The final regression models were evaluated for goodness of fit.

RESULTS

Of the 136 infants 27–33 weeks GA born at a local institution and admitted to the NICU, 36 infants continued to require either mechanical ventilation or non-invasive ventilation beyond 24 hours after birth and were not eligible. Of 100 infants studied, 82 infants developed central apnea during the first two postnatal weeks. The median and mean day for the peak TSB was 3 and 3.7 day, respectively. The median and mean day for the peak UB was 3 and 3.5 day, respectively. There was no significant difference in peak TSB between the group of infants who developed central apnea and the group of infants who did not have central apnea during the first 2 postnatal weeks (9.9 ± 1.8 mg/dL [169.2 ± 30.78 μmol/L] *vs*. 9.6 ± 1.5 mg/dL [164.16 ± 25.6 μmol/L]), respectively. Since the critical value of UB concentration that may be associated with central apnea is not known, we used a median peak UB among study subjects as a cut-off value to define High and Low UB groups. The median peak UB among study subjects was 0.92 μg/dL or 15.73 nmol/L and was used to form two subgroups: High UB group (> 0.92 μg/dL peak UB) and Low UB group (< 0.92 μg/dL peak UB). The High and Low UB groups were then compared for the occurrence and frequency of apnea during the first two postnatal weeks after birth.

Table I gives the demographics and clinical risk factors between the High and Low UB groups. There was no significant difference in peak TSB levels between the two groups

(Table II). The High UB group had significantly lower albumin concentration compared to the Low UB group. None of the infants had an Apgar score < 3 at 5 minutes. There was a significant difference in GA, race, and RDS between the two UB groups. The High UB group infants were less mature and had a higher incidence of RDS compared to infants of the Low UB group. Also, more infants of the High UB group were Caucasians compared to infants of the Low UB group. There was no significant difference in birth weight, gender, antenatal steroid exposure, pregnancy induced hypertension, chorioamnionitis, antenatal magnesium sulfate exposure, mode of delivery, PDA, sepsis, and severe IVH between the two groups.

More infants among the high UB group had central apnea during the first two postnatal weeks compared with the low UB group (Table II). The frequency of apnea was significantly higher among the High UB group compared to the Low UB group. Similarly, the frequency of significant bradycardia was significantly higher among the High UB group compared to the Low UB group. There was also significant difference in the number of infants receiving methylxanthine and respiratory support between the two groups. More infants among the High UB group required methylxanthine therapy and respiratory support than the infants in the Low UB group. The High UB group infants also received methlyxanthine therapy and respiratory support (CPAP and nasal cannula) for a more prolonged period in comparison to the Low UB group infants during the NICU stay.

On negative binomial regression analyses, controlling for GA, race, antenatal steroids, severe IVH, and RDS (potential confounders with p value < 0.15, Table 1), the High UB group was associated with higher frequency of apnea during the first postnatal week (Incidence Rate Ratio:1.8, 95% Confidence Interval [CI]: 1.1–3.0). There was marginal but non-significant association between the High UB group and frequency of apnea during the second postnatal week (Incidence Rate Ratio: 1.8, 95% CI: 0.93–3.5, p = 0.08). The High UB group was also associated with higher frequency of apnea when apnea events during the first two postnatal weeks were combined (Incidence Rate Ratio: 1.9, 95% CI: 1.15–3.1). There was no significant association of race (Incidence Rate Ratio: 0.8, 95% CI: 0.6–1.1), antenatal steroids (Incidence Rate Ratio: 1.3, 95% CI: 0.8–2), severe IVH (Incidence Rate Ratio: 1.7, 95% CI: 0.8–3.5), and RDS (Incidence Rate Ratio: 1.2, 95% CI: 0.8–1.8) with frequency of apnea during the first two postnatal weeks. There was a marginal but non-significant association between GA and frequency of apnea (Incidence Rate Ratio: 0.9, 95% CI: 0.8–1.0, p = 0.06) during the first two postnatal weeks.

The final regression models for each outcome were selected with the lowest quasi likelihood information criterion. There was a significant association between the High UB group and higher frequency of apnea during the first postnatal week (Incidence Rate Ratio: 1.8, 95% CI: 1.1–3.0) after controlling for race, GA, antenatal steroids and severe IVH. There was a marginal but non-significant association between the High UB group and higher frequency of apnea during the second postnatal week (Incidence Rate Ratio: 1.8. 95% CI: 0.98–3.5, p = 0.06) after controlling for RDS, GA and race. When apnea events were combined during the first two postnatal weeks, the High UB group was associated with higher frequency of apnea during the first two postnatal weeks (Incidence Rate Ratio: 1.9, 95% CI: 1.2–3.2) after controlling for race, GA, antenatal steroids, and severe IVH.

DISCUSSION

Our findings strongly suggest that unconjugated hyperbilirubinemia, indexed by UB, is associated with the occurrence and frequency of central apnea, as evaluated by visual inspection of continuous electronic cardio-respiratory waveforms, in 27–33 weeks GA infants. Furthermore, our findings of the need for prolonged respiratory support and methlyxanthine therapy suggest that the adverse influence of jaundice on respiratory control may last for a prolonged period even after the resolution of jaundice.

Respiratory control is mediated by central chemoreceptors present within the brain stem respiratory network that respond to hypoxia and hypercarbia by increasing minute ventilation.(12, 13) Therefore, clinical conditions that cause brainstem injury or dysfunction may be associated with decreased sensitivity to hypoxia and or hypercarbia sufficient to predispose premature infants to central apnea. There is ample evidence in the literature to suggest that unconjugated hyperbilirubinemia may be associated with brainstem injury or dysfunction in neonates.(4, 5, 14– 17) Animal studies and human autopsy studies of kernicterus have consistently shown pathological lesions in the brainstem.(18) Moreover, unconjugated hyperbilirubinemia, indexed by UB, was temporally associated with abnormal ABR progression reflective of brainstem dysfunction or transient bilirubin encephalopathy during the first postnatal week in premature infants ≤ 33 weeks GA.(5) The underlying mechanism of jaundice induced apnea was recently elucidated in an animal study.(19) Mesner et al demonstrated in a study involving rat pups that jaundice blunted the normal hyperventilation response to hypercapnia and hypoxia which may explain the association between jaundice and central apnea.(19

Our findings are consistent with previous reports of the association between unconjugated hyperbilirubinemia and apnea in premature infants.(6, 20) We previously reported that premature infants with transient bilirubin-induced brainstem dysfunction had more concurrent apneic events and required respiratory support and methylxanthine therapy for prolonged duration compared to premature infants without transient bilirubin-induced brainstem dysfunction.(6) However, apnea evaluation was based on a retrospective analysis of nursing documentation of apnea in medical charts which may be inaccurate.(7, 21) Compared to the retrospective study, the present study prospectively evaluated central apnea using more accurate visual inspection and analysis of electronic cardio-respiratory waveforms. Secondly, we found that in addition to the frequency of central apnea, the frequency of significant bradycardia during the first two weeks was also higher among infants in the high UB group compared with the low UB group. More importantly, more infants in the high UB group received respiratory support and methlyxanthine therapy, further validating the association between jaundice and central apnea. In addition, our findings of the need for more prolonged respiratory support and methlyxanthine therapy among infants in the high UB group are also consistent with previous studies.(6, 20) DiFiore et al demonstrated a significant association between unconjugated hyperbilirubinemia and central apnea using 12 hour cardiorespiratory monitoring and inductance plethysomography at a mean age of 8.4 weeks suggesting a long lasting effect of jaundice on respiratory control.(20) These studies together suggest that unconjugated hyperbilirubinemia may be

associated with adverse effects on brainstem mediated respiratory control for a prolonged period.

There is growing evidence to suggest that UB is more strongly associated with bilirubin induced neurotoxicity than TSB.(4–6, 22–24) We previously reported that UB and not TSB is more strongly associated with central apnea.(6) The findings of the current study corroborate this evidence. In the present study, we found no association between TSB and central apnea. Moreover, TSB levels were similar between the two UB subgroups defined based on median peak UB level. However, there was a significant difference in the occurrence and frequency of central apnea during the first two weeks between the two UB groups. Although albumin concentrations were normal, the difference in albumin concentration between the two UB groups may partially explain higher UB concentration in the High UB group compared to the Low UB group. In addition, we speculate that bilirubin binding to albumin may also have been compromised by endogenous or exogenous factors such as free fatty acid concentration, acidosis, etc. Our finding suggests the importance of measuring UB and searching for correctable reasons for high UB.

Central apnea may be associated with adverse long-term neurodevelopmental outcomes.(25–27) Identification of underlying etiology may provide preventive and therapeutic interventions to decrease adverse long-term neurologic outcomes that may be associated with central apnea. Our findings of increased incidence of central apnea with UB of > 0.92 μg/dL for infants 27 to 33 weeks gestation may be generalized and lead to a more function-based approach to the determination of safe levels of UB in premature infants of other GA. Once threshold levels of UB that result in bilirubin-induced neurotoxicity have been determined for different GA, a more rational basis for phototherapy or other effective therapeutic interventions can be developed for premature infants. Aggressive treatment of premature infants with elevated UB to prevent bilirubin-induced brainstem dysfunction may decrease the incidence of apnea and related abnormal neurological consequences.

The strength of the study is the prospective evaluation of central apnea using visual inspection of continuous cardio-respiratory waveforms on a central monitor over the first 2 postnatal weeks after birth in each individual subject. Secondly, the evaluation of apnea was performed by an investigator unaware of bilirubin biochemical measures, including UB levels. Finally, appropriate regression analyses were performed to control for the influence of confounders. In conclusion, our findings from the prospective observational study strongly suggest that bilirubin-induced neurotoxicity may manifest clinically as central apnea in premature infants.

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Abbreviations

GA	gestational age
ABR	auditory brainstem evoked response
NICU	neonatal intensive care unit
CPAP	continuous positive airway pressure
UB	unbound bilirubin
TSB	total serum bilirubin
RDS	respiratory distress syndrome (RDS)
IVH	intraventricular hemorrhage
PDA	patent ductus arteriosus
Kp	first order rate constant

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Table 1

Clinical Profile of Infants as a Function of Unbound Bilirubin

	Low UB Group (n = 50)	**High UB Group (n = 50)**	***P***
Gestational Age (weeks)*	30 ± 1.6	29.4 ± 1.8	0.002#
Birth Weight (g)*	1449 ± 371	1374 ± 391	0.17#
Race (% White)	64	82	0.04
Sex (% Male)	48	60	0.23
Antenatal Steroids (%)	88	76	0.12
Pregnancy Induced Hypertension (%)	20	15	0.48
Clinical Chorioamnionitis (%)	2	8	0.36**
Maternal Magnesium Sulfate (%)	46	40	0.54
Mode of Delivery (% C-section)	18	22	0.84
Respiratory Distress Syndrome (%)	44	70	0.009
Patent Ductus Arteriosus (%)	8	12	0.50**
Sepsis (%)	20	22	0.8
Severe Intraventricular Hemorrhage (%)	2	4	0.13**
Intravenous Lipid Intake First 4 days After Birth (%)	95	95	1

*Mean ± SD;

#Rank sum test;

**Fisher's exact test

Table 2

Central Apnea as a Function of Unbound Bilirubin

	Low UB Group (n = 50)	High UB Group (n = 50)	*P*
Peak Total Serum Bilirubin (mg/dL)*	9.8 ± 1.8	10 ± 1.8	0.40**
Peak Unbound Bilirubin (μg/dL)*	0.64 ± 0.18	2.3 ± 2.6	0.0001#
Albumin (g/dL)	3.3 ± 0.3	3.1 ± 0.3	0.002**
Occurrence of Apnea (%)	70	94	0.0001$
Apnea (# first week)*	4.2 ± 6.5	7.8 ± 8.4	0.002#
Apnea (# second week)*	1.9 ± 3.4	4.8 ± 5.8	0.007#
Significant Bradycardia (# first week)*	2.1 ± 3.6	5.1 ± 7.6	0.008#
Significant Bradycardia (# second week)*	3.8 ± 8.2	6.0 ± 7.0	0.004#
Methylxanthines (%)	48	66	0.06
Duration of Methylxanthines (days)*	8.8 ± 5	13.6 ± 15	0.04
Respiratory Support (Nasal Cannula or CPAP) (%)	66	92	0.003$
Duration of Respiratory Support (CPAP or Nasal Cannula) (days)*	12.4 ± 14.8	23.2 ± 19.6	0.0005#

*Mean ± SD;

**Student t-test;

#Rank sum test;

$Fisher's exact test