Apnea in Acute Bilirubin Encephalopathy

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Abstract

Central apnea, defined as cessation of breathing for ≥20 seconds, is frequent in premature infants born < 34 weeks gestation but uncommon among healthy late preterm (340/7–366/7 weeks gestation) and term (≥37 weeks gestation) infants where it is usually a clinical manifestation of a neurological or metabolic problem. There is growing evidence that marked unconjugated hyperbilirubinemia is associated with central apnea in neonates. This paper explores the reported association between acute bilirubin encephalopathy and symptomatic apneic events in newborns and the possible mechanisms involved in the pathogenesis of this phenomenon. The prevalence of symptomatic apneic events in reports of acute bilirubin encephalopathy suggests this clinical finding should be considered a sign of bilirubin neurotoxicity.

Introduction

Acute bilirubin encephalopathy (ABE) is characterized by progressive disturbances in neurobehavior across time.1,2 The initial signs are subtle and nonspecific but increase in severity and specificity as bilirubin-induced neurologic disturbances evolve.1,2 Early nonspecific findings include lethargy and poor feeding followed by abnormalities of muscle tone (initially hypotonia followed by hypertonia) which progress to the more ominous advanced phases of opisthotonus (truncal arching), retrocolis (neck extension), high pitched cry, fever and on occasion seizures.1,2 These classic clinical findings have been appreciated for decades and the appearance of any advanced phase abnormality is an indication for
double volume exchange transfusion as set forth in the 2004 American Academy of Pediatrics (AAP) practice guideline. Indeed, although the appearance of advanced signs of ABE indicate a high risk of permanent CNS damage, recent case series suggest that aggressive treatment can reverse bilirubin-induced CNS injury and lead to a normal outcome in some circumstances.

Recent reviews of kernicterus cases in term, late preterm and the preterm neonate document symptomatic apneic events as a frequent clinical finding, often in conjunction with other signs of advanced ABE but, on occasion, as an isolated early neurobehavioral abnormality. These observations suggest that apnea is a clinical marker of bilirubin neurotoxicity and should be considered a sign of intermediate to advanced ABE. This review highlights the occurrence of apnea in neonates with ABE.

**Physiology of Respiratory Control**

Apnea refers to a cessation of airflow that results from central and/or obstructive mechanisms. Central apnea, defined as cessation of breathing for ≥20 seconds, is considered a manifestation of developmental immaturity of respiratory control mediated by the brainstem in preterm neonates and disordered respiratory control in term and late-preterm infants with neuropathology. To understand how hyperbilirubinemia might lead to central apnea requires an understanding of the physiology of respiratory control in neonates.

The respiratory control network consists of a long cellular column in the brainstem that extends from the caudal medulla and roof of the 4th ventricle through the ventrolateral medulla, to the dorsolateral pons, and ultimately to the nucleus of the solitary tract. Respiratory control is mediated by coordinated feedback from peripheral chemoreceptors (mainly the carotid bodies) and central chemoreceptors within the brainstem respiratory network that respond to hypoxia, hypercarbia, and/or acidosis. Central chemoreceptors are present at multiple sites within the brainstem including the parafacial respiratory group, nucleus tractus solitarius, locus coeruleus, and the medullary raphe. Existing literature suggests that CO₂ stimulates central chemoreceptors that activate the central pattern respiratory generator in the brain stem. Inhalation of CO₂ results in an increase in minute ventilation (V̇E = respiratory rate X tidal volume) even in the most premature infants. In full term newborns, the slope of the ventilatory response to CO₂ is comparable to that of the adult, but positioned to the left of the adult and shifts to the right with increasing postnatal age. In premature infants, the ventilatory response to increasing CO₂ is blunted and when compared with term infants and adults, the apneic threshold is much closer to eupneic levels of PaCO₂. Thus; premature infants are more prone to apnea than term infants. When symptomatic this is referred to as apnea of prematurity (AOP). The slope of the ventilatory response to CO₂ (CO₂ sensitivity) increases with advancing gestational age. The mechanisms responsible for the increase in CO₂ sensitivity with postnatal maturation remain unclear but do explain the decreased incidence of apnea with maturation in premature infants. The incidence of apnea is highest in the most premature infants, decreasing markedly by 34 weeks postmenstrual age (PMA) and still further by 43 weeks PMA when apnea incidence in premature infants approaches that of the full term infant.
Brainstem Injury with Unconjugated Hyperbilirubinemia

Clinical factors that are associated with brainstem injury or dysfunction may affect chemoreceptors and/or the neural network that controls respiration and might decrease CO₂ sensitivity sufficiently to predispose infants to central apnea. There is ample evidence to suggest that elevated levels of unconjugated hyperbilirubinemia is associated with brainstem injury. Animal and autopsy studies of kernicterus in human neonates have consistently shown pathological lesions that involve the brainstem nuclei, reticular formation of pons, locus coeruleus, and medullary raphe. Term neonates with moderate to severe hyperbilirubinemia demonstrate transient brainstem dysfunction that manifests as changes in the auditory brainstem evoked response (ABER). Increased levels of unbound bilirubin in infants ≤ 33 weeks gestation are also temporally associated with abnormal ABERs suggesting transient bilirubin encephalopathy. Unconjugated hyperbilirubinemia is also associated with an abnormal cry pattern in premature and term neonates, another clinical manifestation of brainstem dysfunction as the muscles involved in cry pattern are controlled by the brainstem nuclei/nerves.

Mechanisms for Hyperbilirubinemia Induced Apnea

In an elegant animal study, Mesner and colleagues elucidated the mechanisms by which bilirubin may alter respiratory control and cause apnea. These investigators infused bilirubin (50 mg/kg) or placebo intravenously in 9-day-old anesthetized rat pups (n = 36). The pups were divided into two groups. In the first group, 18 pups were killed at 10–180 minutes after the end of bilirubin infusion to determine serum bilirubin levels. In the second group, 12 pups (6 treated and 6 placebo controls) were returned to their mother and nursed until 24 hours after the bilirubin infusion when minute ventilation was measured using plethysmography at rest (baseline) and under hypercapnic (10% CO₂) and hypoxic conditions (5% inspired oxygen). The bilirubin levels were as high as 25 mg/dL soon after infusion tapering to < 10 mg/dL at 60 minutes post-infusion. The serum albumin levels of all pups were < 1 g/dL suggesting reduced bilirubin binding capacity and high unbound bilirubin levels. The minute ventilation of the bilirubin treated group was significantly reduced at rest compared with the controls (3.2 ± 0.51 vs. 3.56 ± 0.52 ml/min/g, respectively). All pups responded to hypercapnia by increasing their minute ventilation but this response was significantly diminished in the bilirubin treated pups compared with the controls. On exposure to severe hypoxia, there was a significant increase in ventilation within 2 minutes of exposure which was sustained for 10 minutes among the controls while no similar increase in ventilation occurred in the bilirubin treated pups. Thus, hyperbilirubinemic pups demonstrated both blunted hypercapnic and hypoxic ventilatory responses. Histological examination confirmed bilirubin deposition in the brainstem of the treated pups, specifically on the ventral surface of the medulla. In the absence of hyperbilirubinemia apnea did not occur in 9 day old rat pups strongly suggesting that altered respiratory control is one underlying mechanism of apnea in jaundiced infants. With respect to CNS development, the rat brain at postnatal day 7 to 10 approximates that of the human brain at term gestation.
Apnea as a Clinical Manifestation of Acute Bilirubin Encephalopathy in Late Preterm and Term Infants

The occurrence of apnea in a term infant (≥37 weeks’ gestation) is uncommon and usually heralds underlying neurologic pathology. Recent reviews of kernicterus cases in late-preterm and term infants document symptomatic apneic events as a frequent clinical finding (Table 1)⁶ often in conjunction with other signs of advanced ABE but, on occasion, as an isolated early neurobehavioral abnormality.⁶⁻⁸ Most of these term infants had peak total serum bilirubin > 30 mg/dL.⁶ Apnea may also be a sign of seizures in newborns with jaundice, although only a few infants with apnea during ABE have had seizure activity documented electroencephalographically.⁷,⁸

There is limited data regarding the true prevalence of apnea among late preterm and term infants with severe jaundice (peak total serum bilirubin ≥20 mg/dL). In a retrospective study, Weng and co-workers reported that 2.4% of late preterm and term infants with severe hyperbilirubinemia due to ABO and Rh incompatibility (n=83) had apnea.²⁸ Similarly, Amin et al. found a 5% prevalence of apnea in a prospective study of 100 late preterm and term infants with severe hyperbilirubinemia. All infants who presented with apnea had peak total serum bilirubin levels > 25 mg/dL and had other neurological signs of ABE (unpublished observations).

These observations suggest that symptomatic apneic events are a common clinical sign of bilirubin neurotoxicity in late preterm and term neonates with severe jaundice. In a jaundiced late preterm or term infant, apnea should immediately raise the concern of ABE and a bilirubin level should be obtained in a timely manner. In the context of severe hyperbilirubinemia (defined as TSB > 20 mg/dL) in such infants, one must consider apnea as a sign of ABE and more often than not as a sign of intermediate to advanced stages of ABE. Indeed, in recent case series apnea and periodic breathing feature prominently in many late preterm and term neonates with bilirubin encephalopathy.⁶⁻⁸,²⁹ The occurrence of apnea is also highlighted in the bilirubin-induced neurological dysfunction scoring system as a sign of advanced ABE.⁶ Signs of intermediate to advanced stages of ABE would warrant an urgent double volume exchange transfusion as recommended by the AAP.³

Apnea as a Clinical Manifestation of Acute Bilirubin Encephalopathy in Preterm Neonates <34 weeks gestation

Preterm infants infrequently manifest the characteristic neuromotor signs of ABE observed in term neonates such as hypertonia, opisthotonus and retrocolis, likely because of incomplete myelination of brainstem neuronal circuitry and synaptic organization (Michael Painter, personal communication). Prior reports identified “cyanotic attacks” as a sign of kernicterus in the preterm neonates.³⁰ More recent reports highlight symptomatic apneic events as a frequent clinical sign of ABE in premature infants⁷,⁸,¹⁹ including several case reports of severe apnea in VLBW preterm infants during the newborn period who go on to have chronic bilirubin encephalopathy.⁷,⁸ Some suggest such disordered control of breathing is a “distinctive picture” of ABE in preterm infants or at least a prominent clinical
feature. More convincing evidence for the association between unconjugated hyperbilirubinemia and central apnea is provided by recent clinical studies performed in premature infants.

Amin and colleagues reported an association between ABER progression in hyperbilirubinemic preterm (28–32 weeks gestation) neonates and increased frequency of concurrent apnea and bradycardia events (Table 2). Moreover, this affected subset of infants required more prolonged respiratory support (nasal cannula and nasal CPAP) and methylxanthine treatment than those with normal ABER maturation. The ABER abnormalities, however, were transient, reversible changes that resolved with time as did the apnea of prematurity. Although the association between unconjugated hyperbilirubinemia and apnea was most pronounced during the first postnatal week, the findings that premature infants with transient ABE required respiratory support and methylxanthine therapy for more prolonged duration strongly suggest long lasting effect of bilirubin-induced brainstem dysfunction on control of breathing. Moreover, unbound bilirubin was more closely associated with brainstem dysfunction and central apnea than total serum bilirubin in these premature infants. The major limitation of these studies was that the findings were based on nursing documentation of apnea in medical charts.

In a separate study of very low birth weight premature infants using 12 hour cardiorespiratory monitoring and inductance plethysmography, DiFiore and colleagues demonstrated a significant association between peak total serum bilirubin > 10 mg/dL and persistent apnea of prematurity at ~37 weeks postmenstrual age after controlling for confounding variables in multiple logistic regression. This observation provides additional evidence that unconjugated hyperbilirubinemia may be associated with pronounced disordered control of breathing, long after hyperbilirubinemia has resolved.

The association between jaundice and apnea in premature infants, demonstrated in retrospective studies, was confirmed by Amin et al. in a prospective study of 27 to 33 week gestation premature infants. Central apnea was documented for the first two weeks following birth by visual inspection and analysis of continuous electronic cardiorespiratory and oxygenation waveform on the central monitor which uses impedance technology. Unbound bilirubin (UB) and total serum bilirubin levels were measured twice a day during the first postnatal week and thereafter when clinically indicated at the discretion of the attending neonatologist during the 2nd postnatal week. The study population was divided into two groups based on the median peak UB level and the two groups were then compared for the occurrence and frequency of apnea events during the first 2 weeks, duration of respiratory support, and need for methylxanthine therapy. The UB was measured by an independent investigator blinded to clinical characteristics including apnea events. The findings are shown in Table 3. More infants in the High UB group developed apnea during the first 2 postnatal weeks compared with the Low UB group. The High UB group also had more apnea events during the first two weeks compared with the Low UB group. The association between unconjugated hyperbilirubinemia, indexed by UB, and occurrence and frequency of apnea, remained significant even after controlling for confounders in multiple regression analysis. On regression analysis, controlling for gestational age, race, and respiratory distress syndrome, being in the High UB group was significantly associated with
the frequency of apnea during the first (Coefficient 3.5, p = 0.02) and second (Coefficient 2.2, p = 0.028) week of postnatal life. The High UB group also required more prolonged respiratory support compared with the Low UB group indicating long lasting adverse effect on respiratory control. The findings of this prospective study were consistent with those of earlier retrospective studies and provided further validity to the growing evidence for apnea as one of the clinical manifestations of bilirubin-induced neurotoxicity in premature infants. These findings also suggest that UB is more closely associated with bilirubin-induced neurotoxicity in premature infants than total serum bilirubin.

The clinical challenge is to distinguish between AOP and bilirubin-induced potentiation of disordered control of breathing in a given preterm infant, as both AOP and bilirubin-induced disturbances in control of breathing in the preterm can evolve in tandem, increasing in frequency (and possibly severity) over the 1st several days of life. Clinical findings suggestive of a bilirubin-induced disturbance in control of breathing include: (1) new onset of frequent apnea, bradycardia and desaturations concurrent with marked hyperbilirubinemia; (2) apnea, bradycardia and desaturation that requires intubation and assisted ventilation in an infant with marked hyperbilirubinemia; and (3) acute worsening of apnea frequency and severity from baseline levels in an infant with marked hyperbilirubinemia.

In a jaundiced preterm infant, a notable change in the frequency and/or severity of apnea should prompt a measurement of total serum bilirubin, as this might herald bilirubin encephalopathy. Progression in apnea frequency and severity to the point of requiring intubation and mechanical ventilation in a hyperbilirubinemic infant should be considered a sign of advanced bilirubin encephalopathy and an exchange transfusion be considered in an attempt to avert or attenuate bilirubin-induced CNS damage.

In summary, emerging evidence suggests that bilirubin-induced neurotoxicity resulting from brainstem injury may manifest clinically as symptomatic apneic events. The underlying mechanism appears to be a blunted ventilatory response to PCO$_2$ and or PO$_2$. The clinical manifestations of apnea including their frequency, severity, and persistence in infants with hyperbilirubinemia will depend on the maturity of the neonate, the level of hyperbilirubinemia and the resultant degree of bilirubin-induced brainstem dysfunction or injury. In premature infants, hyperbilirubinemia associated apnea may be more common because of decreased baseline ventilatory response to PCO$_2$ and PO$_2$ resulting in a low baseline apnea threshold coupled with a predisposition to bilirubin induced neurotoxicity at lower total serum bilirubin levels. The growing evidence for the association between hyperbilirubinemia and apnea is largely based on case series and observational studies. Future studies are warranted to further characterize both the relationship between unconjugated hyperbilirubinemia and central apnea and the clinical relevance of symptomatic apneic events to presage intermediate to advanced ABE.

**Acknowledgments**

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References


Table 1

Impact of immaturity and gender on incidence of neonatal apnea as a sign of ABE (n=108) **

<table>
<thead>
<tr>
<th>Associated neonatal apnea</th>
<th>TSB &lt; 35 mg per 100 ml (n=42)</th>
<th>TSB &gt; 35 mg per 100 ml (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>GA ≥ 35 to &lt;37 weeks (n=28)</td>
<td>14/28 (50%)</td>
<td>6/42 (14.3%)</td>
</tr>
<tr>
<td>GA ≥ 37 weeks (n=80)</td>
<td>27/80 (33.8%)</td>
<td>6/42 (14.3%)</td>
</tr>
<tr>
<td>Total (n=108)</td>
<td>41/108 (38%)</td>
<td>14/42 (33.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: ABE, acute bilirubin encephalopathy; GA, gestational age.

Data on presence or absence of neonatal apnea were unavailable for 17 of 125 infants.

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Table 2

Association between bilirubin-induced brainstem dysfunction and apnea in 28–32 week gestation infants: retrospective data.31

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 27)</th>
<th>Bilirubin Encephalopathy (n = 13)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age (weeks)</td>
<td>31.0 ± 0.9</td>
<td>31.0 ± 0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Birth Weight (grams)</td>
<td>1476 ± 277</td>
<td>1480 ± 196</td>
<td>0.9</td>
</tr>
<tr>
<td>Nasal Cannula (days)</td>
<td>2.4 ± 4.2</td>
<td>6.6 ± 7.5</td>
<td>0.02</td>
</tr>
<tr>
<td>CPAP (days)</td>
<td>0.5 ± 1.2</td>
<td>2.2 ± 2.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Methylxanthines (days)</td>
<td>1.9 ± 5.9</td>
<td>9.5 ± 8.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Apnea (# first week)</td>
<td>3.1 ± 7.0</td>
<td>10.8 ± 11.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Bradycardia (# first week)</td>
<td>1.4 ± 2.9</td>
<td>7.6 ± 9.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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Table 3

Association between Unconjugated Hyperbilirubinemia and Apnea in 27–33 weeks GA infants: Prospective Study.\textsuperscript{33}

<table>
<thead>
<tr>
<th></th>
<th>Low Unbound Bilirubin Group (n = 50)</th>
<th>High Unbound Bilirubin Group (n = 50)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age (weeks)</td>
<td>30.5 ± 1.6</td>
<td>29.4 ± 1.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Birth Weight (grams)</td>
<td>1449 ± 371</td>
<td>1374 ± 391</td>
<td>0.17</td>
</tr>
<tr>
<td>Peak Total Serum Bilirubin (mg/dL)</td>
<td>9.7 ± 1.8</td>
<td>10 ± 1.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Peak Unbound Bilirubin (μg/dL)</td>
<td>0.64 ± 0.18</td>
<td>2.3 ± 2.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nasal cannula or CPAP (days)</td>
<td>12.4 ± 14</td>
<td>23 ± 19</td>
<td>0.0005</td>
</tr>
<tr>
<td>Methylxanthine therapy (%)</td>
<td>48%</td>
<td>66%</td>
<td>0.06</td>
</tr>
<tr>
<td>Occurrence of Apnea (%)</td>
<td>70%</td>
<td>95%</td>
<td>0.003</td>
</tr>
<tr>
<td>Apnea (# first week)</td>
<td>4.2 ± 6.5</td>
<td>7.8 ± 8.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Apnea (# second week)</td>
<td>1.9 ± 3.4</td>
<td>4.8 ± 5.8</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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