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Apnea in acute bilirubin encephalopathy

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ABSTRACT

Central apnea, defined as cessation of breathing for ≥20 s, is frequent in premature infants born at <34 weeks' gestation but uncommon among healthy late preterm ($34^{0/7}$–$36^{6/7}$ 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 article 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 non-specific 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), retrocollis (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.[3] 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.[4,5]

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.[6–8] 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.

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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 s, 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.[9,10] 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.[11,12] 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.[13,14] Central chemoreceptors are present at multiple sites within the brainstem, including the parafacial respiratory group, nucleus tractus solitarius, locus coeruleus, and the medullary raphe.[15] Existing literature suggests that CO_2 stimulates central chemoreceptors that activate the central pattern respiratory generator in the brain stem. Inhalation of CO_2 results in an increase in minute ventilation (V_E = respiratory rate X tidal volume) even in the most premature infants.[16] In full-term newborns, the slope of the ventilatory response to CO_2 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 CO_2 is blunted, and when compared with term infants and adults, the apneic threshold is much closer to eupneic levels of $PaCO_2$.[17] 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 CO_2 (CO_2 sensitivity) increases with advancing gestational age. The mechanisms responsible for the increase in CO_2 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.[18]

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 CO_2 sensitivity sufficiently to predispose infants to central apnea. There is ample evidence to suggest that elevated levels of unconjugated hyperbilirubinemia are associated with brainstem injury.[19–24] 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.[24] Term neonates with moderate to severe hyperbilirubinemia demonstrate transient brainstem dysfunction that manifests as changes in the auditory brainstem-evoked response (ABER).[19,21,23] Increased levels of unbound bilirubin in infants born at ≤33 weeks' gestation are also temporally associated with abnormal ABERs, suggesting transient bilirubin encephalopathy.[22] 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.[25]

Mechanisms for hyperbilirubinemia-induced apnea

In an elegant animal study, Mesner et al.[26] 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 2 groups. In the first group, 18 pups were killed at 10–180 min 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 h after the bilirubin infusion, when minute ventilation was measured using plethysmography at rest (baseline) and under hypercapnic (10% CO_2) 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 min 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 min of exposure, which was sustained for 10 min 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. These findings strongly suggest that altered respiratory control is one underlying mechanism of apnea in jaundiced infants. With respect to CNS development, the rat brain at postnatal day 7–10 approximates that of the human brain at term gestation.[27]

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