Bilirubin-Induced Audiologic Injury in Preterm Infants

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KEYWORDS

• Bilirubin • Preterm • Kernicterus • Auditory neuropathy • Hyperbilirubinemia
• Auditory brainstem response • Cochlea • Cochlear nucleus

KEY POINTS

- In preterm infants, bilirubin-induced auditory impairment occurs at total serum/plasma bilirubin (TB) levels that have traditionally been considered safe.
- TB levels do predict auditory manifestations of hyperbilirubinemia in the preterm population. Although unbound or free bilirubin seems to correlates better with clinical presentation, it is not readily available for use as a screening tool in the clinical setting.
- Bilirubin-induced auditory impairment primarily affects brainstem nuclei and the auditory nerve, causing auditory neuropathy spectrum disorder. Auditory brainstem response measurement is the gold standard diagnostic test.
- Although standardized guidelines exist for screening and management of hyperbilirubinemia in infants born at 35 weeks gestational age or later, guidelines for infants born earlier are expert-mediated in the absence of best evidence.

INTRODUCTION

Although hyperbilirubinemia affects most term and late preterm infants in the immediate postnatal period, it is generally modest and of little clinical significance.[1] However, a subset of hyperbilirubinemic infants ultimately experience bilirubin-induced neurologic dysfunction (BIND), a spectrum of neurologic injury that includes classic kernicterus, acute bilirubin encephalopathy (ABE), and isolated neural pathway dysfunction.[2,3]

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The auditory system is particularly sensitive to the effects of bilirubin, ranging from subtle abnormalities in hearing and speech processing to complete deafness.[4–7] Auditory pathway damage may occur at total serum/plasma bilirubin (TB) levels that were previously thought to be harmless and may occur in the absence of other signs of classic kernicterus.[8] In addition, preterm infants may exhibit clinical evidence of kernicterus at normal or marginally elevated TB levels.[9,10] Damage to the auditory system has long-reaching consequences for affected children because language development is intricately tied to auditory function. Even mild-to-moderate hearing loss can significantly affect a child's quality of speech acquisition.[11]

Further complicating the picture is that the current American Academy of Pediatrics guideline for management of hyperbilirubinemia (including the use of phototherapy and exchange transfusion) are for infants at least 35 weeks gestational age (GA).[12–14] Similar evidence-based institutional guidelines are not available for infants less than 35 weeks GA.

This article explores the mechanisms and manifestations of bilirubin-induced damage of the auditory system in preterm infants.

MECHANISMS OF BILIRUBIN-INDUCED NEUROLOGIC DAMAGE

Animal studies have shown that unconjugated bilirubin passively diffuses across cell membranes and the blood-brain barrier, and that bilirubin not removed by organic anion efflux pumps accumulates within the cytoplasm and becomes toxic.[15,16] Exposure of neurons to bilirubin results in increased oxidative stress and decreased neuronal proliferation,[17,18] and presynaptic neurodegeneration at central glutaminergic synapses.[19] Furthermore, bilirubin administration results in smaller spiral ganglion cell bodies, with decreased cellular density and selective loss of large cranial nerve VIII myelinated fibers.[20,21] When exposed to bilirubin, neuronal supporting cells have been found to secrete inflammatory markers that contribute to increased blood-brain barrier permeability and bilirubin loading.[15,16]

The jaundiced Gunn rat is the classic animal model of bilirubin toxicity. It is homozygous for a premature stop codon within the gene for UDP-glucuronosyltransferase family 1 (UGT1A1).[22] The resultant gene product has reduced bilirubin-conjugating activity, leading to a state of hyperbilirubinemia. Studies using this rat model have led to the concept that impaired calcium homeostasis is an important mechanism of neuronal toxicity, with reduced expression of calcium-binding proteins in affected cells being a sensitive index of bilirubin-induced neuronal damage.[23] Similarly, application of bilirubin to cultured auditory neurons from brainstem cochlear nuclei results in hyperexcitability and excitotoxicity.[24]

There is some evidence suggesting that distinct developmental windows exist such that the age at bilirubin exposure is the main determinant of long-term neurologic sequelae because it determines what structures will be actively developing at the time of exposure.[25] Compared with term infants, preterm infants are more prone to neurologic insult in the immediate postnatal period because these insults are more likely to occur during the peak of neural circuit formation. In addition, the sensory pathways undergo myelination earlier and faster than motor pathways, which may partially explain why an auditory-predominant kernicterus subtype is more common in neonates less than 34 weeks GA, in contrast to the classic motor-predominant subtype that is observed in infants born closer to term.[26]