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Bilirubin-Induced Audiologic Injury in Preterm Infants

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Abstract

While hyperbilirubinemia is extremely common among neonates and is usually mild and transient, it sometimes leads to bilirubin-induced neurologic damage (BIND). The auditory pathway is highly sensitive to the effects of elevated total serum/plasma bilirubin (TB) levels, with damage manifesting clinically as auditory neuropathy spectrum disorder (ANSD). Compared to full-term neonates, preterm neonates are more susceptible to BIND and suffer adverse effects at lower TB levels with worse long-term outcomes. Furthermore, while standardized guidelines for management of hyperbilirubinemia exist for term and late-preterm neonates, similar guidelines exist for neonates less than 35 wks gestational age (GA) are limited.

Keywords

Bilirubin; preterm; kernicterus; auditory neuropathy; hyperbilirubinemia; auditory brainstem response; cochlea; cochlear nucleus

Introduction

While hyperbilirubinemia affects the majority of 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 neurological injury including classic kernicterus, acute bilirubin encephalopathy (ABE), and isolated neural pathway dysfunction.[2,3]

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 which were previously thought to be harmless, and may occur in the absence of other signs of classic

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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, as language development is intricately tied to auditory function, and even mild-to-moderate hearing loss can significantly impact a child's quality of speech acquisition.[11]

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

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

Mechanisms of BIND

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 which 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 neurological sequelae as it determines what structures will be actively developing at the time of exposure.[25] Compared with term infants, preterm infants are more prone to neurological insult in the immediate postnatal period as these insults are more likely to occur during the peak of neural circuit formation. In addition the fact that the sensory pathways undergo myelination earlier and faster than motor pathways may partially explain why an auditory-predominant

kernicterus subtype is more common in neonates <34 wks GA, in contrast to the classic motor-predominant subtype that is observed in infants born closer to term.[26]

Preterm infants are particularly vulnerable to BIND

Hyperbilirubinemia is one of many risk factors for neonatal hearing loss, including noisy neonatal intensive care unit (NICU) environments, aminoglycoside exposure, central nervous system (CNS) infection, and hypoxia at birth.[27–29] Prematurity itself is associated with an increased risk neurodevelopmental disability, including sensory and cognitive impairments.[30–32] Preterm infants are at greatly increased all-cause risk of hearing loss when compared with their term counterparts.[33[

Preterm infants are more prone to BIND than their term counterparts for a number of reasons. They are more prone to unconjugated hyperbilirubinemia, as they have increased bilirubin production and a relative deficiency of UGT1A1 expression compared with term infants.[34,35] In addition, they exhibit relatively increased enterohepatic circulation, preventing bilirubin from being eliminated in the stool.[36]

Factors common among preterm infants, such as metabolic derangement, hypoxic-ischemic events and infection, may effectively increase the bilirubin burden in the CNS by increasing the permeability of the blood-brain barrier and independently causing neuronal injury that is further compounded by the oxidative stresses of bilirubin. This may partially explain why preterm infants are more susceptible to bilirubin-induced neurotoxicity than term infants and experience neurological sequelae at lower TB levels.[37–39]

There is evidence that even late preterm infants should not be treated the same as their term counterparts. In a retrospective study with a cohort of 125 infants, near-term neonates (defined as 34(0/7) to 36(6/7) wks) that were treated the same as term infants were found to disproportionately develop kernicterus compared with their term counterparts and experience higher rates of severe post-icteric sequelae (82.7% in late preterm infants compared with 70.8% in term infants, $p<0.01$).[40]

BIND and the Auditory Brainstem Response (ABR)

Brainstem cochlear nuclei are the first structures affected by elevated TB levels, followed by the auditory nerve, with higher neural centers being involved last.[21] The cochlea does not appear to be directly affected by hyperbilirubinemia.[20] However, cochlear damage can occur as a result of the damage to the auditory nerve or cochlear brainstem nuclei,[41] perhaps through loss of transcription factors that these cells provide that are necessary to maintain normal cochlear function.[42]

The auditory brainstem response (ABR) provides an electrophysiologic means of assessing the ascending auditory pathway and localizing the lesion(s). The electric field generated by the compound firing of neurons permits one to track the auditory signal as it travels from the cochlea through each of the brainstem nuclei in sequence.[43–45] Consistent with pathology affecting the brainstem rather than the cochlea, jaundiced Gunn rats have decreased amplitudes of ABR waves II and III (corresponding to waves III and V in the human ABR)

and have increased interwave intervals.[46] They also exhibit decreased amplitude of the binaural interaction component of the ABR, indicating abnormal input to the superior olivary complex.[47] Similar ABR abnormalities in neonates have also been described, and include reduced amplitudes and increased latencies of ABR waves III and V. At higher TB levels, both humans and animal models also demonstrate loss of ABR wave I.[48,49] For example, a study of 37 term infants found that abnormal ABR findings correlated better with "free" or unbound bilirubin (UB) levels >1.0 μg/dL than to TB levels >20 mg/dL.[50,51]

Premature infants are prone to abnormal myelination of the auditory pathway secondary to developmental disruption or various metabolic insults. Neonatal I–V interpeak latency (IPL), an index of auditory nerve myelination at 35 wks GA, was found to have significant correlation with language development at three years of age (as measured using the Preschool Language Scale) in a prospective study of 80 ex-preterm children.[52] Decreasing GA is significantly associated with an increased prevalence of neonatal hearing loss from 1.2% to 7.5% (*i.e.,* diagnostic ABR >35 dB hearing loss) in a study of 18,564 neonates of GA 24–31 wks (p<0.002).[53]

Auditory Neuropathy Spectrum Disorder (ANSD)

ANSD is commonly defined by abnormal auditory neural function (altered or missing ABR waveforms) in the presence of normal cochlear microphonics (the field potential emanating from the receptor potential of hair cells) and otoacoustic emissions or OAEs (sounds emanating from the ear due to non-linear force production by the outer hair cells).[43,44,54–58] Children suffering from ANSD may have pure tone thresholds ranging from mild to profound hearing loss, and the actual threshold levels can vary during sequential tests on different days.[55,59,60] Speech perception is typically worse than would be predicted by pure tone thresholds.[55,59,61] Clinically, patients exhibit difficulties with sound localization or speech discrimination when visual cues are absent.[24]

ANSD is commonly associated with progressive hyperbilirubinemia. Over 50% of children suffering from ANSD have a history of hyperbilirubinemia and/or anoxia in the neonatal period.[62] Nickish, *et al.*[63] found that among 15 children with TB levels greater than 20 mg/dL in the neonatal period, 53% of them were diagnosed with ANSD by ABR testing at a mean age of 5.6 yrs. Conversely, none of 15 children in the control group with normal TB levels had ABR findings suggestive of ANSD at follow-up. Similarly, Saluja, *et al.*[64] found that among a cohort of 13 neonates with hyperbilirubinemia requiring exchange transfusion, 46% had bilateral ABR abnormalities consistent with ANSD. However, while in this study there was no relationship between peak TB level and ANSD, a correlation was found in another study of >600 subjects.[65] Similarly, Martínez-Cruz, *et al.*[66] found that of 102 children who underwent exchange transfusion for hyperbilirubinemia, 15% presented with sensorineural hearing loss by a mean age of 5.5±3.9 yrs; they also had a higher unconjugated serum bilirubin level than their peers without hearing loss. Hearing loss at the time of documented hyperbilirubinemia (defined as serum TB greater than 10–20 mg/dL, depending on the study) was diagnosed by ABR or AABR in 9.0% to 73.3% of children,[64,67–70] although the prevalence of hearing loss later in life (at 2 mos to 2 yrs of age) was only 2%–6.7%.[70–72]

Speech and Language Disorders

While ANSD is the best-characterized auditory manifestation of hyperbilirubinemia, disorders of speech and language have also been described. It is expected that children with ANSD will suffer from language difficulties given that auditory deprivation during the critical period for language acquisition results in central auditory processing and language pathology.[73] Described sequelae include auditory aphasia and imperceptions, word deafness, decreased binaural fusion and auditory learning, and behavioral problems.[24,41,74] Language delay may manifest as subtle learning disabilities and auditory processing problems; however, no correlations between peak TB level or duration of elevated TB exposure in the neonatal period and language delays later in life have been found.[75] In situations where hearing loss occurs as a result of hyperbilirubinemia, the ultimate damage to language skills may be lessened through early identification and management of hearing problems to improve auditory processing and language development.[76,77] Because of the known risk of hearing loss after hyperbilirubinemia, these children tend to be followed with serial audiometry very closely for several years, permitting early diagnosis and aggressive intervention for hearing loss.

The Utility of TB Levels in Screening for BIND

Even in term infants, there is much controversy about what levels of TB are problematic, with thresholds at which treatment is begun ranging between 10–23.4 mg/dL in various studies.[68,71,78–80] A commonly-used threshold in term infants is a TB >20 mg/dL, with 35% of infants above this cutoff experiencing ABR abnormalities.[78] Nevertheless, in multiple cohorts, ABR abnormalities in preterm-to-term neonates (24–42 wks GA) showed no correlation with TB levels.[67,81] In addition to a lack of correlation between ABR findings and TB levels, at least one study has shown no significant correlation between peak TB levels in the neonatal period and childhood language delay in a cohort of preterm infants.[75]

There is a growing body of evidence that UB levels are a better indicator of neurologic dysfunction[82] and auditory system damage[38,39,51] than TB, especially in preterm infants. The UB level describes how much unconjugated bilirubin is not bound to albumin in circulation, and is dependent on factors including the serum albumin level and the affinity of albumin for bilirubin. Preterm infants are more likely to be hypoalbuminemic than their term counterparts, and bilirubin-binding capacity (BBC) is also decreased in neonates who are afflicted with sepsis, hypoxia, or other serious illness.[83,84] BBC was found to be directly proportional to GA in a series of 152 preterm (23–31 wks GA) and very low birthweight (VLBW) infants (<1300 g).[83]

Hypoalbuminemia and sepsis were correlated with the onset of bilirubin encephalopathy at lower TB levels than in neonates without these risk factors (25.4 *vs.* >31.5 mg/dL) in a prospective series of 249 newborns.[85] In addition, a number of commonly-used medications (including sulfonamides, cephalosporins, and beta-lactam antibiotics) have been found to significantly displace bilirubin by preferentially binding to albumin, effectively increasing the UB concentration while maintaining a low TB level.[38] While this is

academically useful information, testing of UB levels is only routinely carried out in a research setting, and there are no existing clinical guidelines allowing the use of UB levels to guide management.

Benefits and Drawbacks of Newborn Hearing Screening

Hearing screening is an important aspect of diagnosing BIND-related auditory damage, with ABR being the test of choice.[68,80,86–88] An ABR test is performed by an audiologist, and involves the presentation of tone stimuli at different frequencies. Electrodes are placed on the head to record the electric field evoked by the sound stimuli. The sound intensity is then varied in order to determine the minimum intensity required to evoke a neural response. This is called “the threshold”. By varying the frequency of the sound stimulus, auditory thresholds can be determined across the frequency spectrum.

Performing a diagnostic ABR as described above is an involved process that can take an hour or more. In order to meet the demand to screen a large number of newborns, the automated ABR (AABR) screening technique has been widely adopted in the US. The AABR test works by presenting click stimuli at a moderately quiet level while the brainstem response is measured. The machine analyzes the response and gives either a “pass” (presence of ABR to the click) or “refer” (absence of ABR and need for a full follow-up diagnostic ABR test). Since the AABR is automated, it is quick and can be performed by a screener who does not need the comprehensive educational background and certification of a pediatric audiologist.

However, the AABR is not perfect and may miss infants with results that are not sufficiently abnormal to trigger a “refer” reading. Additionally, screening tests carried out soon after birth may occur before TB levels have increased to their peak levels and caused hearing loss.[89] This can lead to false negative results, and so these children may not obtain follow-up that may allow diagnosis and treatment of subtle hearing and central auditory processing abnormalities. The prevalence of bilirubin neurotoxicity as a cause of audiological dysfunction may be underestimated if the TB alone is used to assess the severity of newborn hyperbilirubinemia, especially in the preterm population where TB is particularly unhelpful for predicting neurological outcomes.[81]

Despite the drawbacks of automated newborn hearing screening, it remains substantially better than OAE screening, which only tests for cochlear hearing loss. ANSD is usually completely missed by this test and it should not be used to screen children with hyperbilirubinemia.

Is BIND-Induced Auditory Damage Reversible?

There is much interest in the potential for reversibility of BIND-induced auditory dysfunction and there is growing evidence for reversibility of ABR abnormalities in animal models with the administration of albumin infusions.[38,39,90,91] Additionally, mild ABR abnormalities in infants may reverse with intervention by phototherapy and exchange transfusion, and some abnormalities resolve simply with the passage of time. In a prospective study of 56 infants with TB levels of at least 15 mg/dL (compared with 24

infants with normal TB levels), Nakamura, *et al.*[50] found that prolonged latencies of ABR peaks I and V resolved after exchange transfusion. It has been suggested that diagnostic ABR is sensitive to the earliest manifestations of neurotoxicity, and that lowering TB at the time of abnormal ABR may allow only transient toxic neural effects,[8] but there have been no controlled trials to confirm this.

Neonates with ANSD and a history of hyperbilirubinemia are often referred for cochlear implantation. In our experience, this is the one scenario where sensorineural hearing loss may spontaneously reverse. We have seen this occur only twice in over 1300 children evaluated for deafness, with ~90 of them having ANSD.[5,92] Both patients maintained normal OAEs, and experienced full recovery of ABR waveforms before the age of 12 mos. Thus, our typical clinical paradigm is to wait until this age before performing cochlear implantation in any child with ANSD. However, if a child with ANSD loses their OAEs during the first year of life, this indicates that secondary cochlear damage has occurred. In this unfortunate situation, the cochlear hearing loss will not reverse.

Conclusions

BIND-induced auditory damage includes a spectrum of manifestations on the auditory neuropathy spectrum with varying long-term severity, the full extent of which has yet to be fully characterized. Auditory system damage commonly occurs at plasma bilirubin concentrations that are below commonly-used therapeutic thresholds in preterm infants, possibly because the timing of sensory pathway myelination coincides with the immediate postnatal period in these infants. The damage to the auditory system caused by bilirubin in the preterm population is further exacerbated in the presence of concomitant infection, hypoxia, or other metabolic derangements. Guidelines for differential screening of premature infants are not well-defined, and the full impact of hyperbilirubinemia on the preterm population remains largely unknown. In addition to the paucity of literature focusing on preterm infants, most existing studies are observational, relatively small, and lack control groups. While ABR is an imperfect screening tool in this population, there is some evidence that the technique (especially serial ABR screening) may be useful in identifying auditory BIND-induced auditory damage in its earliest stages and preventing long-term neurodevelopmental deficits.

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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; while unbound or “free” bilirubin (UB) appears 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 (ANSD). Auditory brainstem response (ABR) measurement is the gold standard diagnostic test.
- While standardized guidelines exist for screening and management of hyperbilirubinemia in infants born at 35 wks gestational age (GA) or later, such guidelines for infants born earlier are expert-mediated in the absence of best evidence.