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# Audiologic impairment associated with bilirubin-induced neurologic damage

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## SUMMARY

Hyperbilirubinemia is occurs very frrequently among neonates and is usually mild and transient, with no long-lasting sequelae. However, bilirubin-induced neurologic damage may occur in some infants. The auditory pathway is the most sensitive part of the central nervous system to bilirubin-induced toxicity, and permanent sequelae may result from only moderately elevated total serum/plasma bilirubin levels. The damage to the auditory system occurs primarily within the brainstem and cranial nerve VIII, and manifests clinically as auditory neuropathy spectrum disorder.

### Keywords

Bilirubin; Kernicterus; Auditory neuropathy; Hyperbilirubinemia; Auditory brainstem response

## 1. Introduction

Hyperbilirubinemia affects up to 84% of term and late preterm infants in the first week of life [1]. The elevation of total serum/plasma bilirubin (TB) levels is generally mild, transitory, and, for most children, inconsequential. However, a subset of infants experiences lifelong neurological sequelae. Although the prevalence of classic kernicterus has fallen steadily in the USA in recent years, the incidence of jaundice in term and premature infants has increased [2,3], and kernicterus remains a significant problem in the global arena [4]. Bilirubin-induced neurologic dysfunction (BIND) is a spectrum of neurological injury due to acute or sustained exposure of the central nervous system (CNS) to bilirubin. The BIND spectrum includes kernicterus, acute bilirubin encephalopathy, and isolated neural pathway dysfunction [5]. The prevalence of BIND is not well described in the literature because it is difficult to characterize the incidence of CNS dysfunction that may be subtle, transient, and localized [6]. However, the sensitivity of the auditory system to bilirubin is well documented



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and several large observational studies have shown a significant association between hyperbilirubinemia and damage to the auditory system [7–9]. In fact, auditory system damage may occur at TB levels previously thought to be harmless, and may occur in the absence of other signs of classic kernicterus [10]. These auditory effects can range from subtle abnormalities in hearing and speech processing to complete deafness [11–14]. Damage to the auditory system has far-reaching consequences for affected children, as language development is intricately tied to auditory function [15]. This review explores the mechanisms contributing to auditory system damage due to BIND, and describes its manifestations in the pediatric population.

## 2. Cellular mechanisms of BIND

Animal studies have shown that unconjugated bilirubin passively diffuses across cell membranes and the blood-brain barrier (BBB), and bilirubin not removed by organic anion efflux pumps accumulates within the cytoplasm and becomes toxic [16,17]. Exposure of neurons to bilirubin results in increased oxidative stress and decreased neuronal proliferation [18,19] and presynaptic neurodegeneration at central glutaminergic synapses [20]. Furthermore, bilirubin administration results in smaller spiral ganglion cell bodies, with decreased cellular density and selective loss of large cranial nerve VIII myelinated fibers [21,22]. When exposed to bilirubin, neuronal supporting cells have been found to secrete inflammatory markers, which contribute to increased BBB permeability and bilirubin loading [16,17].

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 (*UGT1*) [23]. The resultant gene product has reduced bilirubin-conjugating activity, leading to a state of hyperbilirubinemia. Studies with 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 neurotoxicity [24]. Similarly, application of bilirubin to cultured auditory neurons from brainstem cochlear nuclei results in hyperexcitability and excitotoxicity [6].

## 3. BIND and the auditory brainstem response

Brainstem cochlear nuclei are the first structures affected by elevated TB levels, followed by the auditory nerve, with higher neural centers being involved last [22]. The cochlea does not appear to be directly affected by hyperbilirubinemia [21]. However, cochlear damage may occur as a result of the damage to the auditory nerve or cochlear brainstem nuclei [25], perhaps through loss of transcription factors that these cells provide, which are necessary to maintain normal cochlear function [26].

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 [27–29] (Fig. 1). 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 [30]. They also exhibit decreased amplitude of the binaural interaction component of the ABR, indicating abnormal input to the superior olivary complex [31]. Similar ABR abnormalities in neonates have also been described, and include reduced amplitudes and increased latencies of ABR waves III and V [27]. At higher TB levels, both humans and animal models have also demonstrated loss of the ABR wave I [32,33]. Unconjugated, not conjugated, bilirubin is neurotoxic. For example, a study of 37 term infants found that abnormal ABR findings correlated better with unconjugated bilirubin levels >1.0 g/dL than with TB levels >20 mg/dL [34,35].

## 4. Auditory neuropathy spectrum disorder

Auditory neuropathy spectrum disorder (ANSD) is usually 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 (OAEs, i.e., sounds emanating from the ear due to non-linear force production by the outer hair cells) [27,28,36–40]. Children suffering from ANSD may have pure tone thresholds ranging from mild to profound hearing loss, and the actual threshold level may vary during sequential tests on different days [37,41,42]. Speech perception is typically worse than would be predicted by pure tone thresholds [37,41,43]. Clinically, patients exhibit difficulties with sound localization or speech discrimination when visual cues are absent [6]. ANSD is frequently caused by hyperbilirubinemia. More than 50% of children suffering from ANSD have a history of hyperbilirubinemia and/or anoxia in the neonatal period [44]. Nickish et al. [45] found that among 15 children with TB levels >20 mg/dL in the neonatal period, 53% were diagnosed with ANSD by ABR testing at a mean age of 5.6 years. 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. [46] found that, among a cohort of 13 neonates with jaundice requiring exchange transfusion, 46% had bilateral ABR abnormalities consistent with ANSD. However, in this study, there was no relationship between peak TB levels and ANSD, whereas a correlation was found in another study of >600 subjects [47]. Similarly, Martínez-Cruz et al. [48] 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 years; they also had a higher unconjugated bilirubin level than their peers without hearing loss. Hearing loss at the time of documented hyperbilirubinemia (defined as TB >10-20 mg/dL, depending upon the study) was diagnosed by ABR or an automated ABR (AABR) in 9.0-73.3% of children [46,49–52], although the prevalence of hearing loss later in life (at 2 months to 2 years of age) was only 2-6.7% [52–54].

## 5. Speech and language disorders

Whereas 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 [55]. Described sequelae include auditory aphasia and imperception, word deafness, decreased binaural fusion, and auditory learning and behavior problems [6,25,56]. Language delay may manifest as subtle learning disabilities and auditory processing

problems; however, no correlations between peak TB levels or the duration of elevated TB in the neonatal period and language delays later in life have been found [57]. 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 [58]. 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.

## 6. Utility of TB levels in screening for BIND

There is much disagreement regarding at what levels of TB are problematic, with thresholds at which treatment is begun ranging between 10 and 23.4 mg/dL in various studies [50,53,59–61]. A widely used threshold is TB >20 mg/dL. Although the evidence surrounding its efficacy is conflicting, recent systematic review of the literature supports this threshold, as 35% of infants with TB levels >20 mg/dL experienced transient or lasting ABR abnormalities [59]. Nevertheless, in multiple cohorts, ABR abnormalities in preterm-to-term neonates (24-42 weeks of gestational age) showed no correlation with TB levels [49,62]. Additionally, one large study in neonates with severe hyperbilirubinemia found no difference in TB levels between term neonates with and without abnormal ABR results [60].

There is a growing body of evidence that serum free or unbound bilirubin (UB) levels are a better indicator of neurologic dysfunction [63], and more specifically, auditory system damage [35,64,65] than TB, especially in preterm neonates. The UB level describes how much unconjugated bilirubin is not bound to albumin in the circulation. In an observational study of 191 neonates, Ahlfors et al. [62] found that mean TB levels were not significantly different in babies with and without abnormal ABR results, but that neonates with abnormal ABRs had significantly higher UB levels than their unaffected peers. Although higher TB and UB levels have been associated with worse neurodevelopmental outcomes and higher incidences of hearing loss, ABR abnormalities and hearing loss have been observed in 10-37.5% of neonates with hyperbilirubinemia with a TB level <20 mg/dL, the often-used threshold for initiating treatment [51,53].

## 7. Benefits and drawbacks of newborn hearing screening

Hearing screening is an important aspect of diagnosing BIND-related auditory damage [58], with ABR being the test of choice [50,61,66–68]. An ABR test is performed by an audiologist, and involves the presentation of click stimuli and tone stimuli at different frequencies and intensities to determine the threshold of hearing across the frequency spectrum. It 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 AABR screening technique has been widely adopted in the USA. 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 ABR test). Since this is automated, it occurs quickly and can be performed by a screener.

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 concentration [69]. This may lead to a false-negative results, and cause these children to not obtain follow-up that may allow diagnosis and treatment of subtle hearing and central auditory processing abnormalities. 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.

## 8. Should low-birthweight infants be regarded differently?

Hyperbilirubinemia is one of many risk factors for neonatal hearing loss, including noisy neonatal intensive care unit environments, aminoglycoside exposure, CNS infection, and hypoxia at birth [70–72]. Premature infants have a higher prevalence of these risk factors, are more susceptible to bilirubin-induced neurotoxicity than term infants, and experience neurological sequelae at lower TB levels [64,65,73]. It is thought that premature infants are more susceptible to auditory-predominant kernicterus than classic kernicterus, possibly due to earlier myelination of the auditory pathway than motor pathways. In low birthweight (LBW) infants (<2500 g), the TB level and duration of exposure are positively correlated with the prevalence of hearing loss [74]. Multiple studies have shown a correlation between severe neurological dysfunction and increased TB levels in very low birthweight infants (<1500 g), as well as longer duration of TB elevation in this population [7,75–77]. Guidelines for differential screening of premature infants are not currently well defined, and the full impact of hyperbilirubinemia on the LBW population remains unknown.

## 9. 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 [64,65,78,79]. 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 ≥15 mg/dL (compared with 24 infants with normal TB levels), Nakamura et al. [34] 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 neurotoxic effects [10], 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 >1000 children evaluated for deafness, with ~75 of them having ANSD [12,80]. Both patients maintained normal OAEs, and experienced full recovery of ABR waveforms before the age of 12 months. Thus, our typical clinical paradigm is to wait until this age before performing cochlear implantation in any child with ANSD. However, if children with ANSD lose their OAEs

during the first year of life, this indicates that secondary cochlear damage has occurred. In this unfortunate situation, the cochlear hearing loss cannot be reversed.

## 10. Conclusion

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 may occur at TB concentrations that are below widely used therapeutic thresholds, especially in premature infants and those with comorbidities such as infection and hypoxia. Optimum screening parameters for hyperbilirubinemia are not well defined, as the therapeutic thresholds for TB differ between studies, and there is conflicting evidence for the association between TB levels and BIND. The full scope of long-term auditory damage due to BIND is not well defined, potentially due to many missed cases of subtle hearing and language processing disorders that are not attributed to hyperbilirubinemia in the neonatal period. In general, the literature on this subject is limited in that most studies are observational, and the majority of studies do not include control groups [59]. It is sobering to think of many children with subtle auditory dysfunction who may be missed by current screening and therapeutic criteria. However, there is promising evidence pointing toward the use of ABR to diagnose the earliest stages of auditory damage caused by BIND at a stage where lasting effects may be preventable, or at least reversible.

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## References

1. Bhutani VK, Stark AR, Lazzeroni LC, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr. 2013; 162:477–82. e1. [PubMed: 23043681]
2. Burke BL, Robbins JM, Bird TM, Hobbs CA, Nesmith C, Tilford JM. Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988-2005. Pediatrics. 2009; 123:524–32. [PubMed: 19171618]
3. Village EG. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004; 114:297–316. [PubMed: 15231951]
4. Kaplan M, Bromiker R, Hammerman C. Severe neonatal hyperbilirubinemia and kernicterus: are these still problems in the third millennium? Neonatology. 2011; 100:354–62. [PubMed: 21968213]
5. Bhutani VK, Stevenson DK. The need for technologies to prevent bilirubin-induced neurologic dysfunction syndrome. Semin Perinatol. 2011; 35:97–100. [PubMed: 21641481]
6. Shapiro S, Nakamura H. Bilirubin and the auditory system. J Perinatol. 2001; 21:S52–5. [PubMed: 11803418]
7. Oh W, Tyson JE, Fanaroff AA, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics. 2003; 112:773–9. [PubMed: 14523165]
8. Graziani LJ, Mitchell DG, Kornhauser M, et al. Neurodevelopment of preterm infants: neonatal neurosonographic and bilirubin studies. Pediatrics. 1992; 89:229–32. [PubMed: 1370866]

9. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992-1995. Arch Pediatr Adolesc Med. 2000; 154:725–31. [PubMed: 10891026]
10. Smith CM, Barnes GP, Jacobson CA, Oelberg DG. Auditory brainstem response detects early bilirubin neurotoxicity at low indirect bilirubin values. J Perinatol. 2004; 24:730–2. [PubMed: 15510103]
11. Lin JW, Chowdhury N, Mody A, et al. Comprehensive diagnostic battery for evaluating sensorineural hearing loss in children. Otol Neurotol. 2011; 32:259–64. [PubMed: 21131880]
12. Jerry J, Oghalai JS. Towards an etiologic diagnosis: assessing the patient with hearing loss. Adv Otorhinolaryngol. 2011; 70:28–36. [PubMed: 21358182]
13. Oghalai JS, Chen L, Brennan ML, Tonini R, Manolidis S. Neonatal hearing loss in the indigent. Laryngoscope. 2002; 112:281–6. [PubMed: 11889384]
14. Cristobal R, Oghalai JS. Hearing loss in children with very low birth weight: current review of epidemiology and pathophysiology. Archs Dis Childh Fetal Neonatal Ed. 2008; 93:F462–8.
15. Dlouha O, Novak A, Vokral J. Central auditory processing disorder (CAPD) in children with specific language impairment (SLI). Central auditory tests. Int J Pediatr Otorhinolaryngol. 2007; 71:903–7. [PubMed: 17382411]
16. Brites D, Fernandes A, Falcão AS, Gordo AC, Silva RFM, Brito MA. Biological risks for neurological abnormalities associated with hyperbilirubinemia. J Perinatol. 2009; 29(Suppl 1):S8–13. [PubMed: 19177063]
17. Brites D. The evolving landscape of neurotoxicity by unconjugated bilirubin: role of glial cells and inflammation. Front Pharmacol. 2012; 3:88. [PubMed: 22661946]
18. Brito MA, Lima S, Fernandes A, et al. Bilirubin injury to neurons: contribution of oxidative stress and rescue by glycoursodeoxycholic acid. Neurotoxicology. 2008; 29:259–69. [PubMed: 18164405]
19. Fernandes A, Falcão AS, Abranches E, et al. Bilirubin as a determinant for altered neurogenesis, neuritogenesis, and synaptogenesis. Dev Neurobiol. 2009; 69:568–82. [PubMed: 19449315]
20. Haustein MD, Read DJ, Steinert JR, Pilati N, Dinsdale D, Forsythe ID. Acute hyperbilirubinaemia induces presynaptic neurodegeneration at a central glutamatergic synapse. J Physiol. 2010; 588:4683–93. [PubMed: 20937712]
21. Belal AJ. Effect of hyperbilirubinemia on the inner ear in Gunn rats. J Laryngol Otol. 1975; 89:259–65. [PubMed: 1127320]
22. Uziel A, Marot M, Pujol R. The Gunn rat: an experimental model for central deafness. Acta Otolaryngol. 1983; 95:651–6. [PubMed: 6688323]
23. Ikushiro S, Iyanagi Takashi. UGT1 gene complex: from Gunn rat to human. Drug Metab Rev. 2010; 42:14–22. [PubMed: 19845429]
24. Spencer RF, Shaia WT, Gleason AT, Sismanis A, Shapiro SM. Changes in calcium-binding protein expression in the auditory brainstem nuclei of the jaundiced Gunn rat. Hear Res. 2002; 171:129–41. [PubMed: 12204357]
25. Matkin N, Carhart R. Auditory profiles associated with Rh incompatibility. Arch Otolaryngol. 1966; 84:502–13. [PubMed: 4959429]
26. Maricich SM, Xia A, Mathes EL, et al. Atoh1-lineal neurons are required for hearing and for the survival of neurons in the spiral ganglion and brainstem accessory auditory nuclei. J Neurosci. 2009; 29:11123–33. [PubMed: 19741118]
27. Xia A, Gao SS, Yuan T, et al. Deficient forward transduction and enhanced reverse transduction in the alpha tectorin C1509G human hearing loss mutation. Dis Model Mech. 2010; 3:209–23. [PubMed: 20142329]
28. Oghalai JS. The cochlear amplifier: augmentation of the traveling wave within the inner ear. Curr Opin Otolaryngol Head Neck Surg. 2004; 12:431–8. [PubMed: 15377957]
29. Oghalai JS. Chlorpromazine inhibits cochlear function in guinea pigs. Hear Res. 2004; 198:59–68. [PubMed: 15567603]
30. Diamond I, Schmid R. Experimental bilirubin encephalopathy. The mode of entry of bilirubin-14C into the central nervous system. J Clin Invest. 1966; 45:678–89. [PubMed: 5949114]

31. Shapiro S. Binaural effects in brainstem auditory evoked potentials of jaundiced Gunn rats. Hear Res. 1991; 53:41–8. [PubMed: 2066286]
32. Shapiro SM. Acute brainstem auditory evoked potential abnormalities in jaundiced Gunn rats given sulfonamide. Pediatr Res. 1988; 23:306–10. [PubMed: 3353178]
33. Shapiro SM. Reversible brainstem auditory evoked potential abnormalities in jaundiced Gunn rats given sulfonamide. Pediatr Res. 1993; 34:629–33. [PubMed: 8284101]
34. Nakamura H, Takada S, Shimabuku R. Auditory nerve and brainstem responses in newborn infants with hyperbilirubinemia. Pediatrics. 1985; 75:703–8. [PubMed: 3982902]
35. Funato M, Tamai H, Shimada S, Nakamura H. Vigintiphobia, unbound bilirubin, and auditory brainstem responses. Pediatrics. 1994; 93:50–3. [PubMed: 8265323]
36. Shapiro SM, Bhutani VK, Johnson L. Hyperbilirubinemia and kernicterus. Clin Perinatol. 2006; 33:387–410. [PubMed: 16765731]
37. Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. Auditory neuropathy. Eur Arch Otorhinolaryngol. 1996; 119:741–53.
38. Xia A, Song Y, Wang R, et al. Prestin regulation and function in residual outer hair cells after noise-induced hearing loss. PLoS One. 2013; 8:e82602. [PubMed: 24376553]
39. Choi C-HH, Oghalai JS. Perilymph osmolality modulates cochlear function. Laryngoscope. 2008; 118:1621–9. [PubMed: 18607303]
40. Xia A, Visosky AMB, Cho J-HH, Tsai M-JJ, Pereira FA, OghalaiJ S. Altered traveling wave propagation and reduced endocochlear potential associated with cochlear dysplasia in the BETA2/NeuroD1 null mouse. J Assoc Res Otolaryngol. 2007; 8:447–63. [PubMed: 17701252]
41. Zdanski CJ, Buchman CA, Roush PA, Teagle HFB, Brown CJ. Assessment and rehabilitation of children with auditory neuropathy. Int Congr Ser. 2004; 1273:265–8.
42. Rance G, Beer DE, Cone-Wesson B, et al. Clinical findings for a group of infants and young children with auditory neuropathy. Ear Hear. 1999; 20:238–52. [PubMed: 10386850]
43. Kraus N, Özdamar Ö , Stein L, Reed N. Absent auditory brain stem response: peripheral hearing loss or brain stem dysfunction? Laryngoscope. 1984; 94:400–6. [PubMed: 6700356]
44. Rance G. Auditory neuropathy/dys-synchrony and its perceptual consequences. Trends Amplif. 2005; 9:1–43. [PubMed: 15920648]
45. Nickisch A, Massinger C, Ertl-Wagner B, von Voss H. Pedaudiologic findings after severe neonatal hyperbilirubinemia. Eur Arch Otorhinolaryngol. 2009; 266:207–12. [PubMed: 18560867]
46. Saluja S, Agarwal A, Kler N, Amin S. Auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice. Int J Pediatr Otorhinolaryngol. 2010; 74:1292–7. [PubMed: 20832127]
47. Hulzebos CV, van Dommelen P, Verkerk PH, Dijk PH, Van Straaten HLM. Evaluation of treatment thresholds for unconjugated hyperbilirubinemia in preterm infants: effects on serum bilirubin and on hearing loss? PLoS One. 2013; 8:e62858. [PubMed: 23667532]
48. Martínez-Cruz CF, García Alonso-Themann P, Poblano A, Cedillo-Rodríguez IA. Hearing and neurological impairment in children with history of exchange transfusion for neonatal hyperbilirubinemia. Int J Pediatr. 2014; 2014:605828. [PubMed: 24678325]
49. Ahlfors CE, Parker AE. Unbound bilirubin concentration is associated with abnormal automated auditory brainstem response for jaundiced newborns. Pediatrics. 2008; 121:976–8. [PubMed: 18450902]
50. Jiang ZD, Brosi DM, Wilkinson AR. Changes in BAER wave amplitudes in relation to total serum bilirubin level in term neonates. Eur J Pediatr. 2009; 168:1243–50. [PubMed: 19130081]
51. Guo X, Pu X, An T, Li Q, Qiu M. Characteristics of brainstem auditory evoked potential of neonates with mild or moderate hyperbilirubinemia. Neural Regen Res. 2007; 2:660–4.
52. Sharma P, Chhangani N, Meena K. Brainstem evoked response audiometry (BAER) in neonates with hyperbilirubinemia. Indian J Pediatr. 2006; 73:413–16. [PubMed: 16741327]
53. Wong V, Chen W, Wong K. Short- and long-term outcome of severe neonatal nonhemolytic hyperbilirubinemia. J Child Neurol. 2006; 21:309–15. [PubMed: 16900927]
54. Chen W, Wong V, Wong K. Neurodevelopmental outcome of severe neonatal hemolytic hyperbilirubinemia. J Child Neurol. 2006; 21:474–9. [PubMed: 16948930]

55. Kral A. Auditory critical periods: a review from system's perspective. Neuroscience. 2013; 247:117–33. [PubMed: 23707979]
56. Johnson L, Bhutani V, Brown A. System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr. 2002; 140:396–403. [PubMed: 12006952]
57. Amin SB, Prinzing D, Myers G. Hyperbilirubinemia and language delay in premature infants. Pediatrics. 2009; 123:327–31. [PubMed: 19117899]
58. Moeller MP. Early intervention and language development in children who are deaf and hard of hearing. Pediatrics. 2000; 106:e43. [PubMed: 10969127]
59. Akinpelu O, Waissbluth S, Daniel S. Auditory risk of hyperbilirubinemia in term newborns: a systematic review. Int J Pediatr Otorhinolaryngol. 2013; 77:898–905. [PubMed: 23642487]
60. Boo NY, Rohani AJ, Asma A. Detection of sensorineural hearing loss using automated auditory brainstem-evoked response and transient-evoked otoacoustic emission in term neonates with severe hyperbilirubinaemia. Singapore Med J. 2008; 49:209–14. [PubMed: 18363002]
61. Gupta A, Mann S. Is auditory brainstem response a neurotoxicity marker? Am J Otolaryngol. 1998; 19:232–6. [PubMed: 9692630]
62. Ahlfors CE, Amin SB, Parker AE. Unbound bilirubin predicts abnormal automated auditory brainstem response in a diverse newborn population. J Perinatol. 2009; 29:305–9. [PubMed: 19242487]
63. Daood MJ, McDonagh AF, Watchko JF. Calculated free bilirubin levels and neurotoxicity. J Perinatol. 2009; 29:S14–9. [PubMed: 19177054]
64. Amin SB. Clinical assessment of bilirubin-induced neurotoxicity in premature infants. Semin Perinatol. 2004; 28:340–7. [PubMed: 15686265]
65. Amin SB, Ahlfors C, Orlando MS, Dalzell LE, Merle KS, Guillet R. Bilirubin and serial auditory brainstem responses in premature infants. Pediatrics. 2001; 107:664–70. [PubMed: 11335741]
66. Sheykholeslami K, Kaga K. Otoacoustic emissions and auditory brainstem responses after neonatal hyperbilirubinemia. Int J Pediatr Otorhinolaryngol. 2000; 52:65–73. [PubMed: 10699242]
67. Jiang ZD, Wilkinson AR. Impaired function of the auditory brainstem in term neonates with hyperbilirubinemia. Brain Dev. 2014; 36:212–18. [PubMed: 23587715]
68. Jiang ZD, Liu T, Chen C. Brainstem auditory electrophysiology is supressed in term neonates with hyperbilirubinemia. Eur J Paediatr Neurol. 2014; 18:193–200. [PubMed: 24309481]
69. Shapiro SM, Popelka GR. Auditory impairment in infants at risk for bilirubin-induced neurologic dysfunction. Semin Perinatol. 2011; 35:162–70. [PubMed: 21641490]
70. Coenraad S, Goedegebure A, van Goudoever JB, Hoeve LJ. Risk factors for sensorineural hearing loss in NICU infants compared to normal hearing NICU controls. Int J Pediatr Otorhinolaryngol. 2010; 74:999–1002. [PubMed: 20554331]
71. Yoshikawa S, Ikeda K, Kudo T, Kobayashi T. The effects of hypoxia, premature birth, infection, ototoxic drugs, circulatory system and congenital disease on neonatal hearing loss. Auris Nasus Larynx. 2004; 31:361–8. [PubMed: 15571908]
72. Boo NY, Oakes M, Lye MS, Said H. Risk factors associated with hearing loss in term neonates with hyperbilirubinaemia. J Trop Pediatr. 1994; 40:194–7. [PubMed: 7932930]
73. Watchko J, Oski F. Kernicterus in preterm newborns: past, present, and future. Pediatrics. 1992; 90:707–15. [PubMed: 1408544]
74. Vries LD, Lary S, Dubowitz L. Relationship of serum bilirubin levels to ototoxicity and deafness in high-risk low-birth-weight infants. Pediatrics. 1985; 76:502–13.
75. Xoinis K, Weirather Y, Mavoori H, Shaha SH, Iwamoto LM. Extremely low birth weight infants are at high risk for auditory neuropathy. J Perinatol. 2007; 27:718–23. [PubMed: 17703185]
76. Mazeiras G, Rozé J-C, Ancel P-Y, et al. Hyperbilirubinemia and neurodevelopmental outcome of very low birthweight infants: results from the LIFT cohort. PLoS One. 2012; 7:e30900. [PubMed: 22303470]
77. Moll M, Goelz R, Naegele T, Wilke M, Poets CF. Are recommended phototherapy thresholds safe enough for extremely low birth weight (ELBW) infants? A report on 2 ELBW infants with kernicterus despite only moderate hyperbilirubinemia. Neonatology. 2011; 99:90–4. [PubMed: 20639681]

78. Agrawal VK, Shukla R, Misra PK, Kapoor RK, Malik GK. Brainstem auditory evoked response in newborns with hyperbilirubinemia. Indian Pediatr. 1998; 35:513–18. [PubMed: 10216645]

79. Vinodh M, Ambikapathy P, Aravind MA, Ganesh J. Reversibility of brainstem evoked response audiometry abnormalities at 3 months in term newborns with hyperbilirubinemia. Indian Pediatr. 2014; 51:134–5. [PubMed: 24277970]

80. Lin JW, Chowdhury N, Mody A, et al. Comprehensive diagnostic battery for evaluating sensorineural hearing loss in children. Otol Neurotol. 2011; 32:259–64. [PubMed: 21131880]

**Practice points**

- TB levels should be interpreted with caution in preterm infants, who are more susceptible to the auditory manifestations of hyperbilirubinemia.
- Auditory impairment due to BIND may occur at TB levels that have traditionally been considered safe.
- BIND primarily affects the brainstem causing ANSD. ABR is the gold standard for diagnosis.
- UB levels may be a better predictor of auditory manifestations of BIND than TB levels.

**Research directions**

- Predictive diagnostic tests are needed to define groups at risk for BIND.
- Randomized clinical trials are needed to determine best practices in neonatal screening for BIND.
- Exploration of ABR monitoring of at-risk newborns as an early indicator of neurotoxicity.
- Longitudinal studies are needed to determine the long-term sequelae of TB and UB levels below therapeutic thresholds.

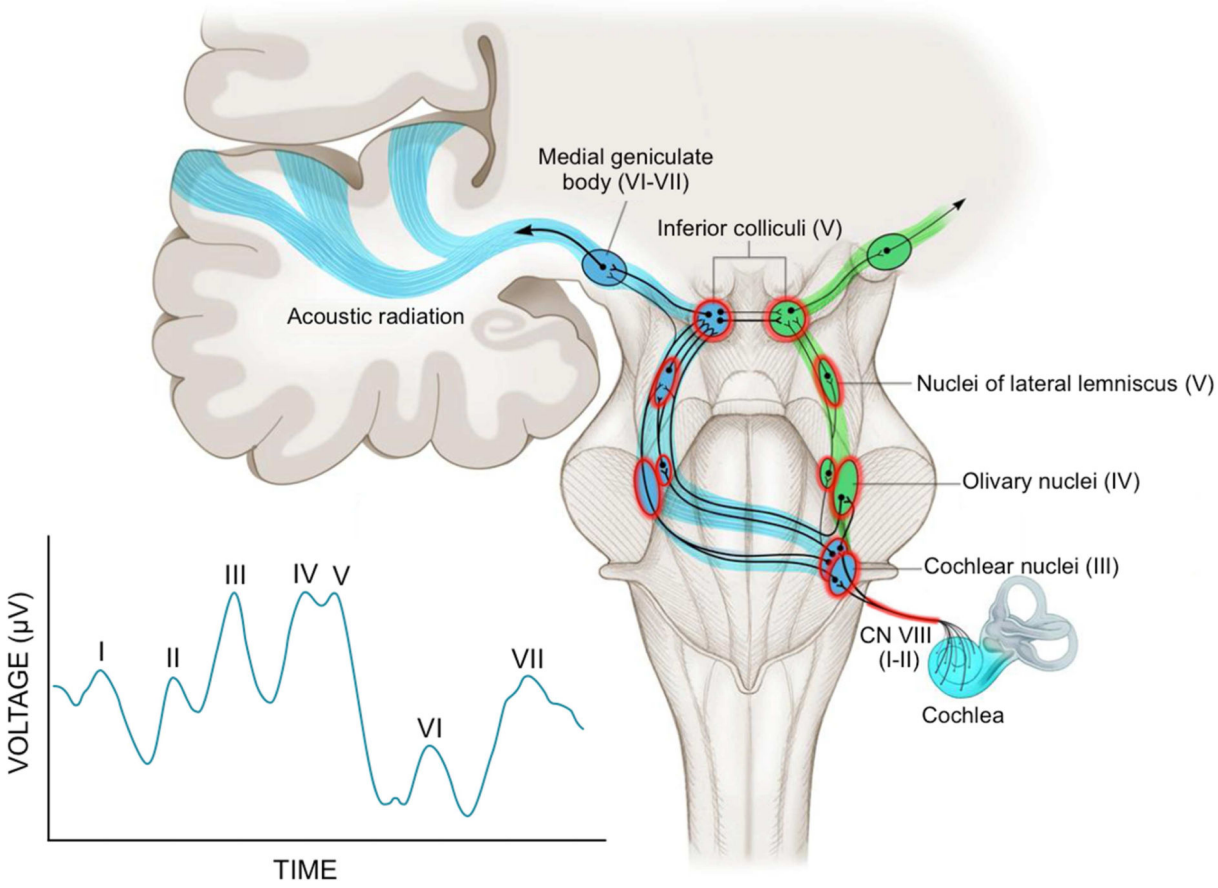


**Fig. 1.**

The auditory pathway and normal auditory brainstem response (ABR). The ipsilateral (green) and contralateral (blue) auditory pathways are shown, with structures that are known to be affected by hyperbilirubinemia highlighted in red. Roman numerals in parentheses indicate corresponding waves in the normal human ABR (inset). Illustration adapted from the “Ear Anatomy” series by Robert Jackler and Christine Gralapp, with permission.