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Review

Audiologic impairment associated with bilirubin-induced neurologic damage

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SUMMARY

Hyperbilirubinemia occurs commonly in 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.

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 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].

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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 μg/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

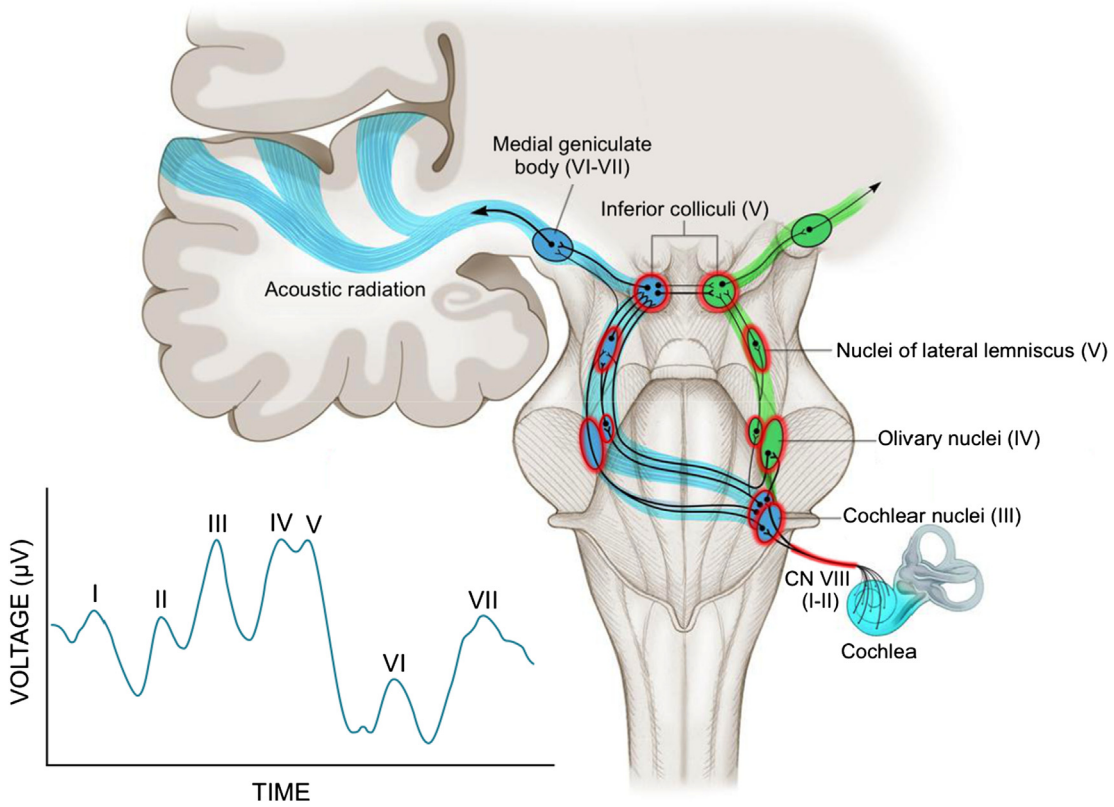

Fig. 1. The auditory pathway and normal auditory brainstem response (ABR). The ipsilateral (green) and contralateral (blue) auditory pathways are shown, with structures that are known to be affected by hyperbilirubinemia highlighted in red. Roman numerals in parentheses indicate corresponding waves in the normal human ABR (inset). Illustration adapted from the "Ear Anatomy" series by Robert Jackler and Christine Gralapp, with permission.