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Review

Movement disorders due to bilirubin toxicity

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SUMMARY

Advances in the care of neonatal hyperbilirubinemia have led to a decreased incidence of kernicterus. However, neonatal exposure to high levels of bilirubin continues to cause severe motor symptoms and cerebral palsy (CP). Exposure to moderate levels of unconjugated bilirubin may also cause damage to the developing central nervous system, specifically the basal ganglia and cerebellum. Brain lesions identified using magnetic resonance imaging following extreme hyperbilirubinemia have been linked to dyskinetic CP. Newer imaging techniques, such as diffusion tensor imaging or single-photon emission computed tomography, allow quantification of more subtle white matter injury following presumed exposure to unbound bilirubin, and may explain more subtle movement disorders. New categories of bilirubin-induced neurologic dysfunction, characterized by subtle bilirubin encephalopathy following moderate hyperbilirubinemia, have been implicated in long-term motor function. Further research is needed to identify subtle impairments resulting from moderate-severe neonatal hyperbilirubinemia, to understand the influence of perinatal risk factors on bilirubin toxicity, and to develop neuroprotective treatment strategies to prevent movement disorders due to bilirubin toxicity.

1. Introduction

Advances in the care of infants with severe hyperbilirubinemia have greatly reduced the incidence of classic kernicterus and possibly of bilirubin-induced neurologic dysfunction (BIND) [1,2]. Despite significant progress, subtle neurological impairments and motor disorders resulting from severe hyperbilirubinemia continue to occur in children around the world. A recent rise in the incidence of kernicterus, after decades of improvement, may be attributable to relaxed standards for initiation of phototherapy, or due to earlier infant discharge from the hospital [1–3]. Furthermore, the subtler symptoms of BIND may be under-recognized and contribute to increased risk of motor impairment such as developmental coordination disorder and learning disabilities [4]. The incidence of kernicterus in the USA is estimated to be 1 in 40,000 births, with about 1 in 650 to 1000 neonates born >35 weeks' postmenstrual age (PMA) experiencing transient hyperbilirubinemia (>25 mg/dL) [5]. Bilirubin has a neurotoxic effect on brain regions including the globus pallidus and subthalamic nuclei, which result in motor-related sequelae ranging from lack of coordination to severe movement disorders such as dyskinetic cerebral palsy (CP). Clinical manifestations of kernicterus vary in form and severity depending on degree of prematurity and stage of regional brain development, degree, and duration of hyperbilirubinemia, as well as other perinatal risk factors such as sepsis, hypoalbuminemia, and genetic predispositions. Regional brain development and vulnerability determine periods during which moderate hyperbilirubinemia could result in auditory versus motor-predominant symptoms of BIND. These manifestations are distinct from those associated with exposure to high levels of neonatal total serum/plasma bilirubin (TB) that are known to cause severe neonatal motor symptoms and long-term sequelae such as dyskinetic CP. This article describes the etiology of the spectrum of motor symptoms and presents emerging evidence on the range of motor outcome that may result from exposure of the developing central nervous system (CNS) to low–moderate levels of TB. Understanding the etiology and scope of motor sequelae is essential to development of neuroprotective treatment protocols and early identification of motor disorders related to moderate–severe hyperbilirubinemia.

2. History of kernicterus and motor impairment

In the mid-twentieth century, the effects of bilirubin on the CNS were substantially unknown and methods to prevent kernicterus

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were limited. Physicians observed significant motor impairments following severe hyperbilirubinemia in neonates and subsequently began to learn how bilirubin specifically targeted motor systems in the developing brain [6]. Classic clinical symptoms of kernicterus included lethargy, high-pitched crying, seizures, eye weakness (ophthalmoplegia), and truncal arching (opisthotonus) [7,8]. Involvement of the CNS suggested that bilirubin was crossing the blood–brain barrier (BBB) and damaging neural structures related to movement. Identifying the causes of hyperbilirubinemia, and some of the related risk factors predisposing infants to kernicterus, helped improve the understanding of the pathophysiology of bilirubin toxicity in the CNS.

3. Neonatal bilirubin metabolism and kernicterus

As the pathobiology of kernicterus became clear, concurrent advances in treatments such as phototherapy helped prevent damage to the developing CNS. Pediatricians monitor TB levels to prevent infants from excess or prolonged exposure to bilirubin. TB is composed of conjugated and unconjugated bilirubin, but in neonates, and particularly those preterm, the unconjugated form dominates due to low activity of the enzyme uridine 5′-diphosphoglucuronosyltransferase (UDPGT), or glucuronyltransferase [7]. As a water-insoluble compound, unconjugated bilirubin travels in the blood bound to proteins such as albumin. The level of albumin is low in the neonate and has a high degree of physiological variation, but increases with gestational age-at-birth and birth weight [9]. When the binding affinity of bilirubin–albumin is decreased, as occurs in medically unstable neonates, or the carrying proteins become saturated, bilirubin exists in its unbound (UB) or “free” toxic form and is able to cross the BBB [10,11]. Albumin-bound bilirubin cannot reach the brain unless the BBB becomes disrupted.

4. Clinical measures of hyperbilirubinemia and BIND

Measuring peak TB may not be the most predictive of outcome. Shapiro [8] and others have suggested that measuring free bilirubin in addition to TB may be important for identifying infants at higher risk for BIND and/or kernicterus. Though difficult, measuring UB may be more prognostic; Oh et al. demonstrated that, in extremely low birth weight (ELBW) neonates, UB is directly related to poor outcomes including CP [11]. Furthermore, UB concentrations are less dependent on clinical status, and thus may be more instructive for clinical decision-making [11]. Among clinically stable neonates, Oh et al. found an inverse relationship between peak TB and incidence of CP or death, suggesting that at moderate levels, bilirubin may have an antioxidant property that provides neuroprotection. More research is needed, however, to understand the possible neuroprotective value of low TB levels.

Measuring the total bilirubin/albumin molar ratio (BAMR) may be more clinically feasible and has been documented to be highly correlated with UB [12]. Furthermore, the BAMR was demonstrated to be more correlated with psychomotor outcome at four years compared to other measures of bilirubin [4]. However, another recent study by Hulzebos et al. [13] found that clinical use of BAMR, instead of TB thresholds, had no effect on neurodevelopmental outcome at 18–24 months of age [13].

Neonatal inflammation and sepsis are known to influence hyperbilirubinemia and subsequent sequelae [14]. During an acute inflammatory response such as neonatal sepsis, albumin production decreases [15]. Neonatal albumin levels have been demonstrated to have an inverse relationship with the inflammatory biomarker, C-reactive protein (CRP), as routinely measured over the first two weeks of life in neonates born preterm with very low birth weight (VLBW) [16], consistent with prior findings. Using diffusion tensor imaging (DTI), Rose et al. [16] also found an association between lower neonatal albumin levels and reduced microstructural development of the thalamus at near-term age, as measured with higher thalamus mean diffusivity (MD) on DTI [16]. Furthermore, lower neonatal albumin levels and higher near-term thalamus MD correlated with poorer motor performance as assessed with Bayley Scores of Toddler and Infant Development, 3rd edition (BSID-III) at 18–22 months of age, adjusted for prematurity (J. Rose et al., unpublished data). Figure 1 shows the inverse relationship between mean neonatal serum albumin levels and near-term thalamus MD. Understanding these associations may provide neonatal clues to mechanisms that mediate later movement disorders related to bilirubin toxicity.

The thalamus is known to be involved in basic motor function and is implicated in kernicterus following hyperbilirubinemia, so the connection between hypoalbuminemia, thalamic microstructural damage, and future motor impairment is plausible from a physiological perspective, and needs further study in larger populations.

5. Severity of hyperbilirubinemia

Whereas identification and treatment of hyperbilirubinemia have resulted in lower rates of severe kernicterus, infants with TB levels previously thought to be safe have been found to exhibit signs of neurological impairment. A safe TB level in neonates has not yet been established, as multiple factors may affect bilirubin–albumin binding and increase an infant's risk for BIND, with relatively low levels of TB. Unconjugated bilirubin is toxic to the developing brain and may be elevated even in the presence of relatively low TB. Several studies have observed increased risk for motor and cognitive impairments following moderate TB levels in neonates [17], though the association between minor neurological/behavioral problems and moderate bilirubin exposure continues to be debated [18].

Cerebral palsy and other movement disorders have been known to occur in children born preterm after exposure to relatively low–moderate levels of TB [3,19]. Though most infants experience a degree of hyperbilirubinemia due to impaired bilirubin–albumin

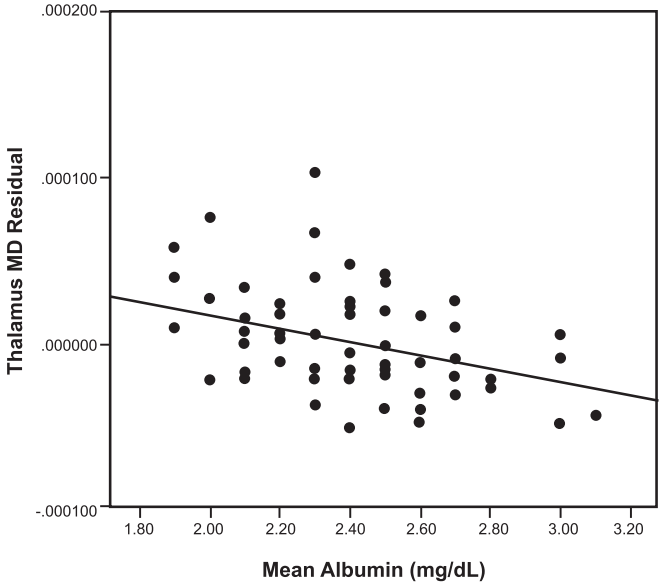

Fig. 1. Near-term right thalamus mean diffusivity, controlling for postmenstrual age at scan, in relation to mean serum albumin, measured over the first two postnatal weeks. $r = -.385$; $P = 0.002$ [16].