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Review

Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes

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SUMMARY

Bilirubin-induced neurologic dysfunction (BIND) is the constellation of neurologic sequelae following milder degrees of neonatal hyperbilirubinemia than are associated with kernicterus. Clinically, BIND may manifest after the neonatal period as developmental delay, cognitive impairment, disordered executive function, and behavioral and psychiatric disorders. However, there is controversy regarding the relative contribution of neonatal hyperbilirubinemia versus other risk factors to the development of later neurodevelopmental disorders in children with BIND. In this review, we focus on the empiric data from the past 25 years regarding neurodevelopmental outcomes and BIND, including specific effects on developmental delay, cognition, speech and language development, executive function, and the neurobehavioral disorders, such as attention deficit/hyperactivity disorder and autism.

1. Introduction

Extreme neonatal hyperbilirubinemia has long been known to cause the clinical syndrome of kernicterus, or chronic bilirubin encephalopathy (CBE). Kernicterus most usually is characterized by choreoathetoid cerebral palsy (CP), impaired upward gaze, and sensorineural hearing loss, whereas cognition is relatively spared. The chronic condition of kernicterus may be, but is not always, preceded in the acute stage by acute bilirubin encephalopathy (ABE). This acute neonatal condition is also due to hyperbilirubinemia, and is characterized by lethargy and abnormal behavior, evolving to frank neonatal encephalopathy, opisthotonus, and seizures. Less completely defined is the syndrome of bilirubin-induced neurologic dysfunction (BIND). BIND is the constellation of neurologic sequelae following milder degrees of neonatal hyperbilirubinemia than are associated with kernicterus. Animal models and basic science research have defined how hyperbilirubinemia may specifically result in later neurodevelopmental impairments [1]. Clinically, BIND may manifest after the neonatal period as developmental delay, cognitive impairment, disordered executive function, and behavioral and psychiatric disorders [2]. In many cases, affected children have multiple risk factors for neurodevelopmental impairment (NDI), including prematurity, perinatal complications, and hemolytic disease. There is controversy regarding the relative contribution of neonatal hyperbilirubinemia versus other risk factors to the development of later neurodevelopmental disorders in children with BIND. Likewise, a number of effect modifiers, such as altered albumin–bilirubin binding and hereditary vulnerabilities, have been proposed. In this review, we focus on the empiric data from the past 25 years regarding neurodevelopmental outcomes and BIND, including specific effects on developmental delay, cognition, speech and language development, executive function, and the neurobehavioral disorders, such as attention deficit/hyperactivity disorder (ADHD) and autism.

2. General neurodevelopment

Numerous retrospective studies have attempted to support or refute the relationship of neonatal hyperbilirubinemia with neurodevelopmental outcomes. A particular challenge in understanding this relationship has been the use of varying measures of neurodevelopment. Developmental delay refers to a failure to achieve developmental milestones in one or more areas by an expected age. Whereas some studies quantify development using validated instruments, such as the Bayley Scales of Infant Development (BSID), others rely on parental report of developmental delay, or do not specify how developmental delay at follow-up was defined. In this section, we include a discussion of studies focused on general neurodevelopment or neurodevelopmental delay as

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outcome measures. These encompass a variety of developmental outcome measures at various ages.

Evidence suggests a relationship between neonatal hyperbilirubinemia and developmental delay, though the association appears complex. A few studies have identified a direct association between hyperbilirubinemia and developmental delay. A cohort study of 50 infants with total serum/plasma bilirubin (TB) > 400 μmol/L (23.4 mg/dL) born in 1991 and 1992 in Bulawayo, Zimbabwe, used the BSID to assess overall neurodevelopment at 1 year of age [3]. This included a mixed population of preterm and term infants with jaundice from multiple causes. The authors found a statistically significant correlation between TB and BSID scores among this group (0.59, $P < 0.001$). Whereas this study is notable for a high rate of hemolytic disease among those infants with the highest TB, the population is perhaps more representative of neonatal hyperbilirubinemia worldwide than those studies conducted in Europe or North America. A larger, population-based study followed all children born in Denmark between 1994 and 2004, again examining the relationship between neonatal jaundice and later developmental delay [4]. This study used diagnosis codes to identify both jaundice exposure and outcomes of disorders of psychological development, including speech/language and learning disorders. Subjects with neonatal jaundice had an increased overall risk of disordered development, with a significant adjusted hazard ratio of 1.29 [confidence interval (95% CI): 1.06–1.56]. This was most pronounced among term newborns ($P < 0.001$). In both these studies, hyperbilirubinemia appeared directly linked to later neurodevelopmental delay. However, further work does not uphold a directly linear relationship between TB and developmental delay.

Several studies have found that hyperbilirubinemia is associated with higher risk of developmental delay, but only in a subset of measures or populations. One historical prospective study compared medical records from the neonatal period and intelligence tests results among 1948 military conscripts in Israel [5]. The authors found that, among term males with TB > 342 μmol/L (20 mg/dL), there was a higher risk of IQ < 85 [odds ratio (OR): 2.96; 95% CI: 1.29–6.79]. The same effect was not demonstrated in females. A retrospective analysis performed by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) examined the association between peak TB and neurodevelopmental outcome at 18–22 months of age among 2575 extremely low birth weight (ELBW) infants [6]. This study found that peak TB directly correlated with significantly lower scores on the psychomotor index of the BSID (OR: 1.057; 95% CI: 1.00–1.12), but no significant association between TB and scores in the mental development index (MDI). Similarly, A population-based study from Nova Scotia examined the relationship between neonatal peak TB and later neurodevelopmental outcome among >50,000 neonates born 1994–2000 [7]. Hyperbilirubinemia was defined as severe if ≥ 325 μmol/L (≥19 mg/dL), moderate if 230–325 μmol/L (13.5–19 mg/dL), or no hyperbilirubinemia if < 230 μmol/L (<13.5 mg/dL). Follow-up times for children ranged from 2 to 9 years, and diagnoses were obtained from data linkage of the study cohort with the national databases on office visits and hospital admissions. This study found a significantly increased risk of developmental delay among children with moderate hyperbilirubinemia as compared to no hyperbilirubinemia, with a relative risk (RR) of 1.6 (95% CI: 1.3–2.0). This remained significant after controlling for other variables. Paradoxically, there was no statistically significant increase in the risk of developmental delay among children with severe hyperbilirubinemia as compared to those without hyperbilirubinemia. The authors do not explain these apparently conflicting findings, though it is notable there were only 348 subjects in the severe hyperbilirubinemia group, which may have affected statistical power. More recently, a study of 631 neonates with two-year follow-up also reported a partial relationship between neonatal hyperbilirubinemia and outcomes [8]. Subjects were divided into tertiles based upon peak TB. Overall, there was no difference in functional outcomes between tertiles. However, among infants with birth weight <1000 g, there was a significantly elevated risk of functional impairment associated with a higher peak TB. These mixed findings suggest that, whereas the relationship between hyperbilirubinemia and later neurodevelopment may not be strictly linear in all groups, hyperbilirubinemia remains a risk factor for at least a subset of newborns.

Other studies have failed to replicate an association between hyperbilirubinemia and developmental delay altogether. Vandborg et al. performed a follow-up study of 206 Danish children with at least one TB > 427.5 μmol/L (25 mg/dL) in the neonatal period [9]. As compared to controls matched for sex, age, and gestational age, there was no significant difference in development as assessed by the Ages and Stages Questionnaire. A smaller cohort study by Heimler et al. followed 39 term neonates with non-hemolytic hyperbilirubinemia; all had TB of 340–513 μmol/L (20–30 mg/dL) [10]. These were compared to 36 healthy controls out to a mean of 3 years of age. Again, there was no significant difference in BSID scores or in speech development between cases and controls. Whereas each of these reports focused on different measures of developmental delay, the overall mixed findings show a need for further rigorous research to clarify the nature of the relationship between hyperbilirubinemia and developmental delay.

3. Cognition

In addition to the data suggesting that hyperbilirubinemia may result in delayed development, there is also controversial evidence that hyperbilirubinemia may lead to overall impaired cognitive ability in some children. Although by no means definitive, cognitive ability is frequently quantified for research purposes in the form of an Intelligence Quotient (IQ). In children, this is now usually measured through the Weschler Intelligence Scale for Children (WISC). To date, there remain conflicting data regarding the effect of hyperbilirubinemia on subsequent IQ.

On the one hand, a biological basis for hyperbilirubinemia affecting cognition is plausible [11]. Similarly, there are some clinical data to suggest a link between neonatal hyperbilirubinemia and later decreased IQ. Most recently, a prospective cohort born 1971–1974 in Helsinki, Finland was followed for 30 years to determine neurobehavioral outcomes [12]. Within the larger overall cohort, the investigators identified 128 cases with neonatal hyperbilirubinemia, defined as TB > 340 μmol/L (20 mg/dL) or requiring exchange transfusion. These were compared to 82 controls. This study only included subjects born at term, with normal birth weight and with no other birth risk factors, in an effort to control for potential confounders. Follow-up was conducted through visits at ages 5, 9, and 16 years, as well as through parental and teacher assessments. IQ testing was performed at age 9 years. At age 30 years, subjects self-reported a number of items via questionnaire. The investigators found that 45% of the cases showed at least one neurobehavioral disability at age 9 years. This was significantly higher than rates in controls, with an OR of 4.8 (95% CI: 2.21–10.11). These difficulties appeared to continue into adulthood. Those cases who had been identified at age 9 years with neurobehavioral disability had lower rates of school completion and lower rates of full-time employment at age 30 years. Ongoing reading difficulties were also significantly more frequent. Whereas the uniform population studied constituted a strength in reducing confounders, it is possible that these results may not be applicable to other populations of jaundiced neonates. A smaller study published in 1991 also found a link between hyperbilirubinemia and intelligence test scores [13]. A cohort of 74 children who required neonatal intensive care were evaluated with a psychoeducational test battery at ages