HHS Public Access

Author manuscript

Semin Fetal Neonatal Med. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

Semin Fetal Neonatal Med. 2015 February ; 20(1): 52–57. doi:10.1016/j.siny.2014.12.003.

Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes

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Abstract

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 th neurobehavioral disorders, such as attention deficit/hyperactivity disorder and autism.

Keywords

hyperbilirubinemia; neonate; outcomes; cognition; developmental disabilities

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

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Conflict of interest statement:
None declared.

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 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 mmol/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 mmol/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 18–22months 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 mmol/L (≥19 mg/dL), moderate if 230–325 mmol/L (13.5–19 mg/dL), or no hyperbilirubinemia if < 230 mmol/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 mmol/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 mmol/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 mmol/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 9 to 11 years. The authors found that direct measures of hyperbilirubinemia, including peak TB, did not have a statistically significant relationship with intelligence outcomes. However, they did find a significant association between a measure of bilirubin-albumin binding and scores on the Kaufman Mental Processing Composite. The authors suggest that the overall TB level may not be as important in determining neurotoxicity as is the free or unbound bilirubin (UB) level, or the bilirubin-albumin binding capacity (BBC). They specifically cite the need for further research to look beyond TB alone.

In contrast to these findings, other studies have not supported the link between hyperbilirubinemia and decreased IQ. Follow-up research after the NICHD Clinical Trial of

Phototherapy measured IQ at age 6 years among 224 neonates with birth weight <2000 g [14]. The authors found no association between peak TB and later IQ, though the study only included neonates with TB levels below exchange transfusion criteria. The largest study to date has been an analysis of US Collaborative Perinatal Project (CPP) data published by Newman and Kleboff in 1993. This study included data from>40,000 children born between 1959 and 1966, with >30,000 of these followed until age 7 years [15]. The authors found no statistically significant relationship between neonatal peak TB level and IQ at age 7 years. This was true both when IQ was dichotomized as well as when it was considered as a linear variable. Strengths of this analysis were the large number of subjects, long duration of follow-up, and thorough statistical analysis to control for confounders. At the same time, this cohort was from an era prior to the use of phototherapy. Given the dates of enrollment, the study may be limited in applicability to neonates receiving current standards of care. Subsequently, Newman et al. also analyzed data from a subset of neonates within a large prospective study of neonates from Northern California [16]. They again found that neonates with peak TB > 428 mmol/L (25mg/dL) did not have significantly different scores on cognitive assessment at a mean of 5 years. All subjects in this study were treated for their hyperbilirubinemia, with the majority having peak TB beyond the threshold for only a few hours. More recently, a retrospective study of Danish male military conscripts found no difference in intelligence test scores between 463 men with neonatal hyperbilirubinemia and controls [17]. Again, there is some concern for selection bias in this study, as those with neurodevelopmental impairment may not have been eligible for conscription. Overall, the evidence does not definitively support a direct link between hyperbilirubinemia and impaired cognition at follow-up. At the same time, the Finnish study in particular raises concern that hyperbilirubinemia may remain one risk factor among many.

4. Language development

Hearing loss is a common feature of kernicterus, and carries with it the expected challenges in language and speech development. In contrast, despite evidence that the auditory system is particularly sensitive to bilirubin neurotoxicity, limited studies to date have not demonstrated a clear relationship between hyperbilirubinemia and speech or language delay.

In the Danish study [4], the authors did investigate whether neonates with hyperbilirubinemia were at high risk for later diagnosis of specific developmental disorders of speech and language, as noted by ICD-10 code in their medical records. That study did find an increased risk among term neonates, with an adjusted hazard ratio (HR) of 1.56 (95% CI: 1.01–2.40). However, there was no statistically significant risk among preterm infants.

In contrast, a case-control study of 102 premature infants with birth weight <1500 g aimed to determine whether either peak TB or number of days with TB > 137 mmol/L (8mg/dL) was associated with a subsequent diagnosis of language delay by 3 years of age [18]. Logistic regression demonstrated no statistically significant relationship; rather, only the presence of bronchopulmonary dysplasia was associated with language delay. Similarly, Heimler et al. [10] also demonstrated no significant relationship between hyperbilirubinemia and speech delay in their cohort of term newborns.

5. Executive function

As outlined above, studies have focused on general cognition or intellectual capacity as measured by IQ as one main outcome measure. It has been proposed that IQ data are limited in identifying the widespread effects of bilirubin neurotoxicity and that BIND may have effects on other cognitive skills including executive function and related domains such as learning and academic achievement [2]. The limitations of focusing only on IQ include varying thresholds across infants in sustaining irreversible brain injury secondary to bilirubin neurotoxicity; the variation in clinical manifestations across infants, including sparing of IQ despite sustaining hearing loss and choreoathetosis; and the possibility of children predisposed to higher IQ having lowered scores that are still within the average range [2]. The study of cognitive skills besides IQ, such as executive functions, might reveal additional effects of BIND.

Executive function is an umbrella term that refers to multiple component skills; among them are: working memory -- the ability to hold information in mind despite competing information or while manipulating other information; shifting or cognitive flexibility -- the ability to switch back and forth between different tasks; and response inhibition -- the ability to suppress a reflexive action in order to do what is desired or needed; and planning [19,20]. Executive function skills are used to regulate and direct goal oriented behavior. There is much interest in executive functions as they have been linked to important functional domains such as academic skills [21–23], adaptive function [24,25], and social competence [26] in both typical and clinical populations. Deficits in executive function have been found in children with history of preterm birth [25–27], ADHD, autism, and learning disabilities [28,29]. Although studies on bilirubin neurotoxicity have not focused on executive functions per se, some studies have identified attention problems [7] and lower academic achievement in children with hyperbilirubinemia [12], two domains affected in other clinical populations at high risk for executive function impairment.

In addition to overlap of clinical manifestations, there is potential overlap in the brain regions or neural networks affected by bilirubin neurotoxicity and those subserving executive functions. Bilirubin neurotoxicity affects a number of structures, including the basal ganglia, central and peripheral auditory pathways, hippocampus, diencephalon, subthalamic nuclei, mibrain, pontine nuclei for respiratory, neurohumoral and electrolyte control, brain stem nuclei for oculomotor and auditory function, and the cerebellum[2]. Executive functions have been link ed in particular to prefrontal cortex, although other regions including the parietal and temporal cortices, basal ganglia, and cerebellum have been identified depending on the specific executive function skill measured on neuropsychological testing or brain imaging [30,31]. Focusing on the basal ganglia and cerebellum, researchers have postulated that movement and action control underpin executive functions, hence abnormalities of both motor control and executive functions are at risk in populations such as children with neonatal jaundice [11]. Although long implicated in motor control, activation of the cerebellum has been identified on neuroimaging studies in association with tasks that tap executive function skills [32]. Given the widespread networks implicated in executive functions, it is plausible that bilirubin neurotoxicity affects similar structures.

In addition to gray matter, white matter integrity may play a role in executive function skills. Mild and moderate-to-severe white matter abnormalities on neonatal magnetic resonance imaging(MRI) have been implicated in executive function impairments in preterm children at age 4 years [33]. White matter fractional anisotropy measured on diffusion tensor imaging has also been associated with behavioral symptoms of inattention and anxiety in school-age children and adolescents born preterm [34]. Future studies utilizing brain imaging to examine inattention and executive functions may help delineate the clinical manifestations of BIND and possible underlying neurobiologic mechanisms.

6. Behavioral disorders

6.1. ADHD

Studies thus far on an association between attention problems or ADHD and hyperbilirubinemia have been mixed. A critical review of earlier studies of full-term infants without hemolytic disease was reassuring, finding no adverse effects of bilirubin on IQ, neurologic examination, or hearing, although ADHD or attention symptoms were not highlighted [35]. In light of a recent study suggesting association of hyperbilirubinemia with attention problems [7], Kuzniewicz et al. further investigated associations between TB levels in infancy and subsequent risk of ADHD in a cohort of term and late preterm infants born from1995 to 2004 in a large health maintenance organization in northern California [36]. Linking laboratory, demographic, and outpatient visit databases, they found no association between TB levels and ADHD diagnoses, controlling for race, gender, birthweight, gestational age, facility of birth, and maternal age.

Recent studies have found associations between hyperbilirubinemia and ADHD, suggesting that further investigation is warranted. The population-based cohort study of healthy term and late preterm infants born in Nova Scotia compared infants with severe hyperbilirubinemia to infants with less severe hyperbilirubinemia or no hyperbilirubinemia at any time in the neonatal period on a variety of adverse outcomes [7]. The severe hyperbilirubinemia group showed a significant increase in the risk of ADHD [adjusted relative risk (RR): 1.9; 95% CI: 1.1–3.3], but the less severe group did not. The study had no cases of kernicterus and no increased risk of CP, deafness, or visual abnormalities.

The Finnish birth risk cohort described above assessed a variety of outcomes, including symptoms of inattention and hyperactivity/impulsivity [12]. In this longitudinal study, children were assessed at ages 5 and 9 years with direct assessment as well as parent questionnaires; 15% had hyperactivity and attention deficit [12]. Children were classified as having (affected) or not having (unaffected) different developmental disorders at age 9 years in both the hyperbilirubinemia and control groups, and these dichotomized groups were used to evaluate risk associated with hyperbilirubinemia at age 30years in comparison with controls. The affected hyperbilirubinemia group scored higher for childhood inattention compared to both the unaffected hyperbilirubinemia and control groups, and also higher for childhood hyperactivity/impulsivity compared to controls. The unaffected hyperbilirubinemia group scored higher in childhood inattention compared to the controls. By adulthood, there were no significant differences among groups for current ADHD symptom rating scales or for self-reported psychiatric problems [12].

6.2. Autism

Recent studies of possible associations between hyperbilirubinemia and autism spectrum disorders also show mixed results. In the aforementioned population-based cohort study from Nova Scotia, there was a non-significant increase in autism associated with the moderate (>230 mmol/L or >13.5 mg/dL) and severe (>325 mmol/L or >19 mg/dL) hyperbilirubinemia groups (adjusted RR: 1.6; 95% CI: 1.0–2.5) [7]. A case-control study nested within the cohort of singleton term infants born between 1995 and 1998 at a northern California Kaiser Permanente hospital identified 338 children with autism spectrum disorder (ASD) diagnosis in outpatient databases and 1817 controls without an ASD diagnosis [37]. Approximately 28% of case and control subjects had one or more bilirubin tests in the first 30 days of life. Compared with children with a maximal bilirubin level of <15 mg/dL (257 mmol/L), children with any degree of TB elevation had no increased risk of ASD after adjusting for gender, birth facility, maternal age, maternal race/ ethnicity, maternal education, and gestational age.

In contrast with these findings, a population-based matched case-control study of 473 children with autism and 473 matched controls born from 1990 to 1999 in Denmark found an almost four-fold risk for infantile autism in infants with hyperbilirubinemia after birth (OR: 3.7; 95% CI: 1.3-10.5) [38]. Stratified analyses showed that this effect was limited to term infants. There were no associations of autism with low Apgar scores, acidosis, or hypoglycemia. A population-based follow-up study of all children born in Denmark between 1994 and 2004 found that exposure to jaundice in neonates was associated with increased risk of infantile autism in children born at term (OR: 1.67; 95% CI: 1.03–2.71) [4]. The study used diagnoses of jaundice from birth and hospital registers rather than TB levels and did not control for important confounds such as maternal education and breastfeeding, factors associated with autism and jaundice, raising questions about the significance of the association [39]. However, a subsequent meta-analysis of 13 studies of neonatal jaundice and ASD found an association between elevated TB and ASD, with an OR of 1.43 (95% CI: 1.22–1.67), suggesting that there is a true link between these conditions [40].

7. Implications and future research directions

As noted in a technical report by the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, “it is apparent that the use of a single total serum bilirubin level to predict long-term outcomes is inadequate and will lead to conflicting results” [41]. As described above, this has certainly been the case in research to date. To clarify how hyperbilirubinemia influences neurodevelopmental outcome, more sophisticated consideration is needed both of how to assess bilirubin exposure leading to neurotoxicity, and of those comorbid conditions which may lower the threshold for brain injury.

For example, premature infants are known to be especially susceptible to bilirubin neurotoxicity, with kernicterus reported following TB levels far lower than the threshold expected in term neonates [42]. Similarly, among extremely preterm neonates, BBC is proportional to gestational age, meaning that the most premature infants have the highest UB, even for similar TB levels [43]. Thus, future studies must be adequately powered to examine preterm infants separately from term infants, and should consider not just peak TB,

but also BBC, as independent variables in neonates with hyperbilirubinemia. Similarly, an analysis by the NICHD NRN found that, among ELBW infants, higher UB levels were associated with a higher risk of death or NDI [44]. However, increased TB levels were only associated with death or NDI in unstable infants. Again, UB or BBC appeared to be more useful than TB.

At the same time, carefully designed research is needed to disentangle the role of prematurity, hemolysis, and hyperbilirubinemia in neonates at risk for NDI. In addition to the above concerns of how prematurity may play a role, the cause of hyperbilirubinemia may be important in the risk of neurotoxicity. Whereas Newman et al., 's 2006 study found no difference in cognitive outcomes between neonates with or without hyperbilirubinemia, it was noted that, within the group of neonates with hyperbilirubinemia, those with a positive direct antiglobulin test (DAT) had lower cognitive scores [16]. Similarly, in re-analysis of the CPP data, Kuzniewicz and Newman found a statistically significant interaction between positive DAT and peak TB ≥ 428 mmol/L (25 mg/dL) on IQ scores [45]. These results are especially important in view of the high rates of hyperbilirubinemia due to hemolysis worldwide [46].

Given the potential scale of disease of BIND on a global level, there remains a need to understand how hyperbilirubinemia impacts neurodevelopmental outcomes outside of frank kernicterus. Well-designed prospective studies are needed; these must include measures not only of TB, but also of UB in the neonatal period. Analyses must control for gestational age, birth weight, and cause of hyperbilirubinemia. Finally, longer term follow-up using validated outcome measures or objective proxies (such as MRI) are essential. Outcome measures must go beyond IQ to assess impairment accurately. Similar to the preterm population, children with hyperbilirubinemia may have IQ in the normal range despite other adverse outcomes, although at the group level scores may be skewed. Executive function measures, both parent report and direct assessment, could reveal other cognitive deficits that are also linked to poorer outcomes in important functional domains such as learning, academic achievement, adaptive and social function, as well as behavioral and developmental disorders.

8. Conclusions

BIND following relative neonatal hyperbilirubinemia may manifest as a variety of neurodevelopmental difficulties, including developmental delay, cognitive impairment, disordered executive function, and behavioral and psychiatric disorders. Observational data have implicated neonatal hyperbilirubinemia with an increased risk of later NDI, though these findings have not always been replicated in later studies. It is apparent that a linear relationship does not exist between neonatal TB and the risk of BIND; rather, other measures of hyperbilirubinemia (such as UB or BBC) may be more relevant. Similarly, a variety of compounding risk factors may be relevant for any given child's risk of NDI; the interplay of these is not well understood. Further research is needed to elucidate causative factors and potential interventions to prevent NDI in BIND.

Acknowledgments

Funding sources

This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, under the Mentored Patient-oriented Research Career Development Award Grant #K23HD071971 (I.M.L.).

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Practice points

- BIND may manifest after the neonatal period as developmental delay, cognitive impairment, disordered executive function, or behavioral or psychiatric disorders.
- UB and BBC may be more important in evaluating neonates at risk than simply measuring TB.
- TB levels should be interpreted with caution in preterm infants, who are more susceptible to the neurodevelopmental impairment due to hyperbilirubinemia.
- Follow-up of neonates at risk for BIND should incorporate neurodevelopmental assessments that go beyond IQ measurements, including considerations of executive function, ADHD, and the possibility of ASD.
- Subtle neurodevelopmental impairment due to BIND may occur at TB levels that have traditionally been considered safe.
- BIND may impact multiple neurosensory processing functions.
- Elucidation of neonatal jaundice history and of prematurity could be useful in children with impaired cognitive skills.
- Clinical biomarkers for manifestations in BIND have yet to be validated.

Research directions

- The role of UB on neurodevelopmental outcomes following neonatal hyperbilirubinemia.
- The risk of BIND specifically following hemolysis, which still causes a significant global burden.
- Validation of early biomarkers of neurotoxicity, including that in subtle neurodevelopmental impairment.