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REVIEW ARTICLE

Developmental influence of unconjugated hyperbilirubinemia and neurobehavioral disorders

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Bilirubin-induced brain injury in the neonatal period has detrimental effects on neurodevelopment that persist into childhood and adulthood, contributing to childhood developmental disorders. Unconjugated bilirubin is a potent antioxidant that may be useful for protecting against oxidative injuries, but it becomes a potent neurotoxin once it crosses the blood brain barrier. Because bilirubin toxicity involves a myriad of pathological mechanisms, can damage most types of brain cells, and affects brain circuits or loops that influence cognition, learning, behavior, sensory, and language, the clinical effects of bilirubin-induced neurotoxicity are likely to be manifold. One possible effect that several experts have identified is bilirubin-induced neurological dysfunction (subtle kernicterus). However, the underlying biological mechanisms or pathways by which subtle kernicterus could lead to developmental disorders has not been elucidated previously. Our aim in this review is to describe a spectrum of developmental disorders that may reflect subtle kernicterus and outline plausible biological mechanisms for this possible association. We review existing evidence that support or refute the association between unconjugated hyperbilirubinemia and developmental disorders, and limitations associated with these studies.

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INTRODUCTION

Unconjugated hyperbilirubinemia (UHB) is one of the most common problems during the first 2 weeks after birth among premature and term infants and warrants timely evaluation and management to prevent bilirubin-induced brain injury. Studies amply document the neurotoxic effects of unbound unconjugated bilirubin (UB, bilirubin not bound to protein).[1–4] Bilirubin-induced neurotoxicity (kernicterus) occurs when UB crosses the blood–brain barrier. Bilirubin has a predilection for specific brain areas including the basal ganglia, cerebellum, brainstem nuclei, peripheral and central auditory pathways, and hippocampus.[3,4] In these areas, bilirubin may compromise multiple developmental processes including neurogenesis, myelination, and synaptogenesis during early human brain development.[2,4] Thus, the characteristic clinical manifestations of kernicterus that are routinely described and are consistent with neuropathological findings include athetoid cerebral palsy, paralysis of upward gaze, and hearing disorders.[4–6] However, these may represent "the tip of the iceberg." In fact, several experts have suggested that subtle kernicterus or bilirubin-induced neurological dysfunction (BIND) without the frank characteristic clinical findings of kernicterus may be more common (Fig. 1).[7–10] The BIND spectrum may encompass multiple overlapping and comorbid neurodevelopmental disorders (NDDs), including cognitive delay, attention deficit hyperactivity disorder (ADHD), specific learning disorder (SLD), autism spectrum disorder (ASD), and/or language disorder (LD).[5,7,9–13] Evidence for a link between the BIND and NDDs comes from observational studies. However, plausible biological mechanisms for this link have not been fully articulated, and the quality of evidence has not been carefully evaluated. The current review aims to fill these gaps in the literature.

PATHOGENESIS OF BILIRUBIN-INDUCED COGNITIVE DELAY, ADHD, ASD, SPECIFIC LEARNING DISORDER, AND LANGUAGE DISORDER

Bilirubin-induced cerebral cortex injury

There is both in vitro and in vivo evidence demonstrating that UHB may result in damage to cortical neurons. There is also some evidence to suggest that the cortex is relatively less susceptible as compared to other regions such as cochlear nucleus or cerebellum.[2,14] Although the bilirubin-induced injury to cortex may not be readily apparent by gross histopathology or light microscopy, electron microscopy, and immunohistochemistry analyses have both demonstrated abnormalities indicative of damage to cortical neurons.[4,14] The effects of bilirubin on cortical neurons include a reduction in neurite extension and dendritic and axonal arborization as well as increased cell death by apoptosis. This would contribute to dysfunction within various corticocortical and cortico-subcortical circuits. Moreover, a reduction in dendritic arborization is a hallmark feature of many NDDs.[15] Furthermore, based on in vitro and in vivo models, Brites et al. have reported that moderate-to-severe UHB may impair the development and maturation of neurons, glial cells, and oligodendrocytes and have a significant impact on crucial brain functions such as cognition.[2,12,16–18]

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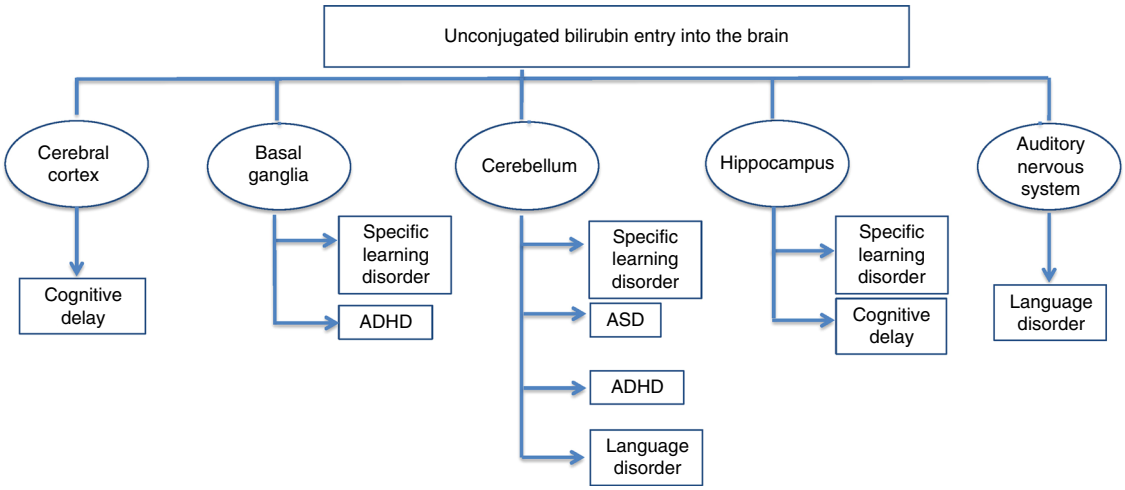

Fig. 1 Bilirubin-induced neurological dysfunction: clinical pathological correlates of bilirubin-induced injury to specific brain areas

Bilirubin-induced basal ganglia injury

Basal ganglia refers to a group of subcortical nuclei that can be broadly categorized as input nuclei (striatum), output nuclei (globus pallidus interna and substantia nigra pars reticulate), and intrinsic nuclei (globus pallidus externa, subthalamic nucleus, and substantia nigra pars compacta). The input nuclei receive incoming information from different sources including cortex and thalamus, while output nuclei send information to the thalamus. Neuropathologic studies have consistently shown that bilirubin induces injury to the globus pallidus (both the internal and external segments) and subthalamus.[3,4,19,20] These structures play a critical role in regulating cognition and behavior via five parallel and segregated cortico-striatal-pallidal-thalamic-cortical circuits.[21] The prototypic connections of all circuits begin in the frontal lobes and project from there as follows: frontal lobes → striatum (caudate, putamen, ventral striatum) → globus pallidus → specific thalamic nuclei → cortex (Fig. 2). There are both direct and indirect pathways within each circuit. The direct pathway (unbroken line, Fig. 2) directly links striatum to globus pallidus interna whereas the indirect pathway (dashed lines, Fig. 2) arrives at the globus pallidus interna through the following path: striatum → globus pallidus externa → subthalamus nucleus → globus pallidus interna. The spontaneous firing of the globus pallidus interna inhibits the thalamus tonically and prevents the thalamus from activating the cortex. Activation of the direct pathway inhibits the activity of the thalamus, thereby releasing (or decreasing) tonic inhibition on the cerebral cortex and increasing behavior.[21] By contrast, activation of the indirect pathway increases the tonic inhibitory activity of the thalamus on the cortex thereby suppressing behavior.[21] Furthermore, a hyper-direct pathway (thick lines, Fig. 2) connects the cortex to subthalamus. Activating a hyper-direct pathway results in more activity in the subthalamus, which then leads to tonic inhibition of the thalamus via activation of globus pallidus interna. Therefore, bilirubin-induced injury involving the subthalamus may result in impulse and stimulus bound behavior commonly seen in children with ADHD.[22,23] The cortico-striatal-pallidal-thalamic-cortical circuits are also critical for a range of non-hippocampal learning and memory functions, including the acquisition of motor skills and perceptual-motor learning (e.g., writing), stimulus-response learning, reward-based learning and grammar and thus may contribute to a variety of symptoms/disorders ranging from clumsiness (impaired motor incoordination) to specific language impairment.[24–26] Thus depending on where damage or dysfunction is incurred within the cortico-striatal-pallidal-thalamic-cortical circuits, it would be possible to experience inhibition or disinhibition of cognitive, motor, and behavioral functions, leading to a range of cognitive and behavioral symptoms ranging from decreased psychomotor processing speed to hyperkinetic/stimulus-bound behavior.

Fig. 2 Cortico-striatal-pallidal-thalamic-cortical circuit. The unbroken lines denote direct pathway. The dashed lines denote indirect pathway. The thick lines denote a hyper-direct pathway. The plus sign denotes increase (or activation) and the minus sign denotes decrease (or inhibition). The spontaneous firing of the globus pallidus (GP) interna inhibits the thalamus tonically and prevents the thalamus from activating the cortex. Activation of direct pathway inhibits the tonic inhibitory activity of thalamus on cortex thereby increasing behavior. Activation of indirect pathway or hyper-direct pathway increases the tonic inhibitory activity of thalamus on cortex thereby suppressing behavior

In addition to well-described segregated corticostriatal-pallidal-thalamic-cortical circuits, specific integrative networks function with parallel circuitry. This interaction between circuits allows flow of information and integration between limbic/emotional/motivational and cognitive/motor circuitries critical for generating and executing goal-directed behavior as well as modifying existing behavior and learning new skills. As globus pallidus and subthalamus are an integral part of these integrative networks,

bilirubin toxicity can potentially affect the learning of novel cognitive skills and manifest as a SLD. Globus pallidus-cortical interactions are also crucial for the function of working memory, which predicts performance in real-word cognitive tasks.[11,27,28] Working memory depends on cortical storage of multiple representations, plans, and ideas in the prefrontal-parietal lobe circuits and prevention of intrusions or distractions mediated by globus pallidus-cortical interactions.[27,28] Working memory, which is the ability to carry and utilize information in the mind that is no longer present in the environment, is required for many forms of learning, including mathematics.[29–31]

In summary, depending on the area of basal ganglia involvement from bilirubin injury, clinical features of ADHD, SLD, and executive dysfunction may manifest.

Bilirubin-induced cerebellar injury

Bilirubin-induced cerebellar injury has been described in neuropathological reports.[3,4] The cerebellum is heavily interconnected with both the cerebral cortex and the basal ganglia via the cerebro-ponto-cerebellar-thalamo-cortical-pathways as well as the other cerebello-cortical pathways and numerous reciprocal basal ganglia cerebellar connections.[25] The reciprocal connections between cerebellum and basal ganglia are important because injury to either one can contribute to similar neurodevelopmental impairments.[25] As described for basal ganglia, there is growing evidence for cerebellum involvement in cognition and behavior. The cerebellum is important for optimal neurodevelopment, and cerebellar injury during the perinatal period can have long-lasting effects on cognition and behavior.[32–34] For example, cerebellar dysfunction has been implicated in ADHD and dyslexia.[33–37] The impairment of the cerebellar component of cerebro-cerebellar circuit (cortex→pons→cerebellum→thalamus →cortex) has also been linked to disturbances in executive function and working memory.[38,39] Cerebellar dysfunction has also been linked to linguistic deficits including disruption of language pragmatics, verbal fluency, phonological and semantic word retrieval, expressive and receptive syntax, and impairment in reading and writing.[40]

Based on new insights in cerebellar function, specifically anatomical and functional interactions between the cerebellum and cerebrum, and known neuropathological findings of bilirubin-induced cerebellar injury, the underlying putative mechanism for the possible association between UHB and ASD was first described by Amin et al.[9] Cerebellar abnormalities are commonly observed among children with ASD. The autopsies of autistic children have shown cerebellar hypoplasia involving both vermis and cerebellar hemispheres with significantly decreased number of purkinje and granule cells of cerebellum.[9] Various anatomical, neuroimaging, and electrophysiological studies suggest that the cerebellum is actively involved in spatial attention and sensory function. Consistent with these studies, bilirubin-induced cerebellar injury could disrupt multisensory cerebellar-cerebral feedback loop, contributing to the clinical characteristics of ASD.[9]

Bilirubin-induced hippocampal injury

Bilirubin-induced injury is associated with greater reduction in dendritic and axonal arborization in the hippocampus than in cortex.[2] Hippocampus is critical for declarative memory and injury to hippocampus profoundly impair recent memory critical for learning new task (or information) or learning how to navigate one's environment.[41] Learning and memory require rapid and persistent changes (also referred as synaptic plasticity) in hippocampal neuronal circuits.[42] Hippocampal cells "learn" to encode the key features of experience and this rapid and persistent neuronal encoding is a crucial step toward the formation of long-term memory. Bilirubin-induced injury to the hippocampus during the neonatal period may adversely influence synaptic plasticity and therefore may lead to memory deficits with profound implications on cognition and learning abilities necessary for academic performance.[4,43–45]

Bilirubin-induced auditory nervous system injury

The auditory neural system consists of an intricate set of neural connections interposed between hierarchically arranged nuclei. The ascending pathways carrying sound information from the cochlea to the auditory cortex are negatively altered from injury to auditory structures such as auditory nerve and cochlear nuclei. Furthermore, auditory nervous system development is intricately related to subsequent language development and auditory sensory deprivation during critical periods of brain development has been demonstrated to increase the risk of LD.[13,46–48] Neuropathological studies and neonatal clinical studies have consistently shown that bilirubin has specific predilection to brainstem auditory structures, including cochlear nuclei, superior olivary complex, lateral lemniscus, and inferior colliculus which are components of central auditory nervous system.[4,49] Therefore, bilirubin-induced auditory nervous system dysfunction during the critical period of brain development may adversely influence subsequent language development.[13]

CLINICAL STUDIES OF THE ASSOCIATION BETWEEN UHB AND NDDS

Global cognitive functioning

Premature infants have an increased risk for cognitive delay reported as high as 30%; however, the underlying modifying risk factors are unknown.[50–55] Premature infants have a higher prevalence of UHB and the available evidence suggest that premature infants may be more susceptible to neurotoxic effects of bilirubin than term infants.[4,49,56] Although the association between UHB and cognitive delay is biologically plausible, data regarding the association between UHB and cognitive delay, that is, lower measured intelligence quotient (IQ) relative to same-age peers, are conflicting. The National Institute of Child Health and Human Development phototherapy trial, which involved preterm and term infants, failed to demonstrate any significant difference in mean IQ at 6 years of age despite lower mean peak total serum bilirubin (TSB) in the phototherapy group versus control group.[57,58] However, in subgroup analysis of white children with birth weight <2000 g ($n = 155$), children exposed to phototherapy for 96 h had significantly higher verbal IQ score than the control group (104.2 vs. 99.2).[57] In another subgroup analysis of 224 control infants (not exposed to phototherapy) with birth weight <2000 g, of which 24% had received exchange transfusion, the authors reported no association between UHB, indexed by peak TSB, and IQ at school age.[59] However, 42% of the sample was lost to follow-up at 6 years of age, a major limitation reported in these studies.[57,59] Several other observational studies, mainly involving late preterm and term infants or low birth weight (LBW) infants, have also failed to demonstrate an association between UHB and IQ.[60–68] However, in a larger Helsinki study, infants with TSB > 20 mg/dL or who received exchange transfusion ($n = 244$) had significantly lower performance IQ compared to control infants ($n = 44$) when evaluated at 9 years of age.[69] Several other studies involving preterm and/or term infants had findings that suggest hemolysis or infection-associated UHB may lead to cognitive delay.[70–76] Among late preterm and term infants with TSB ≥ 25 mg/dL, 9 infants with hemolysis (direct antiglobulin test [DAT] positive) had significantly lower IQ than infants without hemolysis.[71] The adjusted absolute differences between the 2 groups were −18.3 (95% CI, −26.6 to −10.1) for verbal IQ, −12.0 (95% CI, −21.3 to −2.8) for performance (non-verbal) IQ, and −17.8 (95% CI, −26.8 to −8.8) for full-scale IQ when evaluated at 5 years of age.[71] In a separate study involving 56 infants ≥36 weeks gestational age (GA) with peak TSB ≥ 25 mg/dL who participated in the Collaborative Perinatal Project, 19 DAT positive infants had

significantly lower IQ at 7 years of age in comparison to 37 DAT negative infants.[74] In addition, in a Norwegian study involving 39 male infants born at 28–42 weeks GA, 7 infants with a positive DAT and UHB for ≥5 days had lower mean IQ scores than the national average at 18 years of age.[76] Male predisposition for cognitive delay has also been reported among full-term neonates with UHB and negative DAT.[77] Seidman et al. reported that the risk for IQ <85 was significantly higher ($p = 0.014$) among full-term male but not female subjects with TSB > 20 mg/dL (odds ratio, 2.96; 95% CI, 1.29–6.79).[77] It is unclear why hemolytic jaundice and male gender are risk factors for cognitive delay among children with UHB. Despite the association between UHB, as indexed by TSB, and cognitive delay being controversial, limited studies suggest that UB could be critical in evaluating the association between UHB and cognitive delay.[78,79] In an observational study involving 74 Neonatal Intensive Care Unit graduates, there was a significant association between bilirubin albumin binding measure, an indirect measure of UB, but not peak TSB, with scores on the Kaufman Mental Processing Composite at 9–11 years of age.[79] Similarly, Odell et al. found no significant association between peak TSB and cognitive dysfunction; however, they reported a significant association between salicylate saturation index, an indirect measure of UB, and abnormal cognition at 4–7 years of age.[78]

Attention deficit hyperactivity disorder

ADHD is the most common neurobehavioral disorder, affecting ~8% of children in the United States.[80,81] Most studies have reported two-to-three fold increased risk of ADHD in very premature infants, yet the underlying modifying risk factors are unknown.[52,54,80,82–84] As conveyed in sections "Bilirubin-induced basal ganglia injury" and "Bilirubin-induced cerebellar injury", the association between UHB and ADHD has a great deal of biological plausibility due to bilirubin-induced basal ganglia and cerebellar dysfunction.[11] Sparse evidence from animal and human neonatal studies also suggests that UHB may be associated with ADHD.[85–87] In a large population-based cohort study ($n = 94{,}914$), Wei et al. reported that neonatal jaundice was associated with a significant higher risk for ADHD (adjusted hazard ratio [HR] 2.53; 95% CI: 2.23–2.98) after controlling for gender, urbanization, age at follow-up, newborn respiratory conditions, infections, preterm birth, LBW, other birth conditions, and G6PD deficiency.[85] ADHD was diagnosed by a psychiatrist according to the *Diagnostic and Statistical Manual for Mental Disorders–Fourth Edition* criteria. Although, the GA and the birth weight of subjects were not reported, the adjusted HR for the preterm/LBW population (HR 2.83, 95% CI: 1.55–5.19) was higher than non-preterm/non-LBW population (HR 2.51, 95% CI: 2.20–2.86) after controlling for confounders. The study also demonstrated that subsequent risk of ADHD increases with a longer follow-up period in children with jaundice (Adjusted HR 2.41 at ≤6 years versus adjusted HR 2.76 at ≥6 years). Phototherapy, an index of severity of jaundice, was associated with a higher risk for ADHD than no phototherapy (adjusted HR 1.25; 95% CI:1.07–1.47), suggesting that the degree of jaundice may be critical for evaluating the association with ADHD. In a large population-based cohort study, Jangaard et al. also reported a significant increase in the risk of ADHD (adjusted relative risk 1.9; 95% CI:1.1–3.3) among ≥35 weeks GA healthy infants with TSB ≥19 mg/dL.[87] Limitation of the study was that only 71.2% of subjects were followed ≥4 years of age. There has only been one study demonstrating a lack of association between UHB and ADHD in infants with GA ≥34 weeks and birth weight ≥2000 g. This retrospective study linked laboratory, demographic, and outpatient visit databases of infants from 1995 to 2004 in the Northern California Kaiser Permanente Medical Care Program and investigated the association between child's maximum reported TSB levels in the first 30 days after birth and ever having an outpatient clinic visit at least once at or after 3 years of age with a diagnosis of ADHD assessed using the *International Classification of Diseases, 9th Revision* codes.[88] The study had limitations as the diagnosis of ADHD is difficult in preschool age children.[11,81]

Specific learning disorder

Premature infants are at greater risk for SLD; however, underlying, modifying neonatal risk factors are not known.[89–92] A recent meta-analysis of 14 studies on academic achievement reported that very preterm and/or very LBW children scored 0.60 standard deviations (SD) lower on mathematics tests, 0.48 SD lower on reading tests, and 0.76 SD lower on spelling tests than term-born peers.[82] In addition to strong biological plausibility, the limited existing evidence suggests a possible association of UHB with SLD. Using a teacher questionnaire, Michelsson et al. reported that the frequency of poor total school marks and amount of extra help by class teacher, special education teacher, and speech-language pathologist at 9 years was significantly higher among infants with TSB > 20 mg/dL or those who had exchange transfusion for UHB ($n = 256$) compared to control subjects ($n = 72$).[69] A similar group of term infants with TSB > 20 mg/dL were followed for their neurobehavioral outcome at 9 years of age and educational outcome at 30 years of age.[93] Neurobehavioral disability was seen at 9 years of age among 57 out of 128 children with UHB compared to 12 out of 82 children in the control group without UHB (odds ratio 4.6, 95% CI: 2.2–10.1). The UHB group was sub-grouped as affected UHB group (with neurodisability, $n = 57$) and unaffected UHB group (without neurodisability, $n = 71$) and compared with the unaffected control group ($n = 70$). There were no significant differences in peak TSB or duration of UHB between the two UHB subgroups.[93] The affected UHB group performed significantly poorly on the cognitive test and on tests of writing and reading compared to the unaffected UHB group and the unaffected control group at 9 years of age.[93] The frequency of remedial instruction until 9 years of age was significantly higher in affected UHB group (86%) compared to both the unaffected UHB group (44%) and the unaffected control group (28%).[93] In addition, the affected UHB group scored significantly higher (i.e., more inattention and hyperactivity/impulsivity symptoms) on the ADHD symptom rating scales than the unaffected control group.[93] At 30 years of age, the affected UHB group had a history of significantly lower mean school grades, and smaller potential to graduate from secondary or tertiary education compared to the other two groups.[93] These results indicate long-lasting effects of UHB on learning skills, which may place these children at a disadvantage when seeking future employment.

Autism spectrum disorder

Several observational studies have evaluated the association between UHB and ASD.[87,94,95] Our published meta-analysis of 13 reported observational studies strongly suggests that UHB is associated with ASD (OR: 1.43, 95% CI: 1.22–1.67).[9] Additionally, Maimburg et al. and Sugie et al. reported a dose–response relationship between UHB and ASD further supporting the likely association.[96,97] Since the publication of the meta-analysis, additional observational studies have reported the association between UHB and ASD in a diverse group of population.[98–100] However, most observational studies were retrospective and included infants >34 weeks GA, which is a subject population in which TSB concentration has high sensitivity but low specificity for BIND.[49,101,102] A longitudinal study in premature infants is in progress to evaluate the association between UHB and ASD as a function of UB.

Language disorder

Premature infants are at higher risk for LD with the reported prevalence in school age children born prematurely being ~20%.[103–105] There is considerable evidence that the auditory system is the most sensitive neural system to overt bilirubin

toxicity in preterm and term infants.[4,49] Several studies have demonstrated that UHB may be associated with transient auditory and/or brainstem dysfunction, auditory neuropathy spectrum disorder, or sensori-neural hearing loss (SNHL), which leads to auditory sensory deprivation.[6,49,106–117] Auditory development is complexly related to language development and auditory sensory deprivation during early sensitive periods of brain development has been shown to increase risk for LD.[46–48,118–122] Additionally, neonatal or early auditory dysfunction as evaluated by ABR has been associated with LD at later ages.[46,47,123] Therefore, UHB may be associated with LD as a corollary. In addition, as noted above, damage to basal ganglia and/or cerebellum may also contribute to developmental LDs and thus may explain the incidence of LDs in children with otherwise normal hearing. Previous kernicterus reports have strongly suggested that LD is a common manifestation of bilirubin-induced neurotoxicity.[5–7] In preterm infants, there was no association between UHB and LD when using TSB as a biochemical measure;[13] however, our recent pilot study in 24–33 weeks GA infants strongly suggested that UB may be critical in evaluating the association between UHB and LD (unpublished). Also, literature from the pre-phototherapy era carries some evidence supporting the usefulness of UB. In a longitudinal observational study, Johnson et al. reported that 30–41 weeks GA infants exposed to TSB in the range of 20 mg/dL demonstrated a high incidence of deficit in central auditory perception and language functions at 4 and 7 years of age despite normal cognition and hearing.[7] The audiological and language deficits, as indicated by deficient performance on norm-referenced receptive and expressive language tests were far more evident at 7 years (33%) than at 4 years (15%) due to increased brain maturation, i.e., the gap between developmentally expected, and actual language skills was greater among older children. More importantly, the authors reported a highly significant association of low bilirubin binding reserve (evaluated using HABA binding method for indirect estimation of UB) and not peak TSB with abnormal language functions at 7 years of age after controlling for known confounders such as prematurity, perinatal, and neonatal clinical factors, family history of LD, maternal education, and socio-economic status. Thus, the current limited literature suggests that UHB may be associated with LD and that the optimal age to evaluate this association may be at ≥7 years of age when language skills evolve from sentence level to discourse level capacities such as in narrative production.

DISCUSSION

In summary, because of the myriad of pathological mechanisms involved in bilirubin toxicity; susceptibility of neuronal, oligodendrocytes, and glial cells to bilirubin toxicity; and involvement of brain areas that are an integral part of various circuits or loops that influence cognition, learning, behavior, sensory, and language, the clinical effects of bilirubin-induced neurotoxicity extend far beyond kernicterus. Our review demonstrates that multiple observational studies show an association between UHB and NDDs, providing evidence for a BIND spectrum. Most of these studies involved late preterm and term infants and there is scarce literature concerning premature infants. Furthermore, most studies have focused on a single NDD. However, the complex pathogenesis and multitude of pathways involved with bilirubin-induced neurotoxicity indicate that the occurrence of developmental disorders of BIND is unlikely to be an all-or-none phenomenon. A child may have one or more developmental disorders of the BIND spectrum, depending on the timing, degree, and duration of unbound unconjugated hyperbilirubinemia, susceptibility of specific brain area at the time of UHB, co-morbidity that can influence local neuronal and oligodendrocyte susceptibility, and potential for repair and inherent brain plasticity during early brain development. Current literature suggests that future well-designed and adequately powered prospective longitudinal studies should not only evaluate the independent association of UHB with each NDD, but also evaluate a possible comorbidity of multiple NDDs in the BIND spectrum using appropriate statistical analyses and power. Such studies will help define subtle kernicterus or BIND spectrum and the relative incidence of each NDDs that may be associated with bilirubin-induced neurotoxicity. The NDDs included in BIND spectrum often coexist among school aged children, indicating a possibility of common etiology for these disorders when present simultaneously. Furthermore, most studies have used TSB as the primary biochemical measure of UHB to evaluate the association with NDDs of BIND. However, because recent studies have demonstrated that UB but not TSB is associated with early clinical manifestations of bilirubin-induced neurotoxicity, UB will be critical in evaluating the association between UHB and later clinical manifestations of bilirubin-induced neurotoxicity, specifically NDDs of BIND.[111–115,117,124–126] In the absence of UB, lack of association between UHB (indexed by TSB) and NDDs of BIND should be viewed as inadequate evidence for refuting the association. A carefully planned prospective longitudinal study is urgently needed to study BIND or subtle kernicterus at an appropriate age as a function of neonatal unbound unconjugated hyperbilirubinemia.

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ADDITIONAL INFORMATION

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