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Review

The clinical syndrome of bilirubin-induced neurologic dysfunction

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SUMMARY

Clinicians have hypothesized a spectrum of minor neurologic manifestations, consistent with neuroanatomical reports and collectively termed as a "syndrome of bilirubin-induced neurologic dysfunction (BIND)," which can occur in the absence of classical kernicterus. The current review builds on these initial reports with a focus on clinical signs and symptoms that are assessed by standardized tools and manifest from neonatal age to childhood. These clinical manifestations are characterized by the following domains: (i) neuromotor signs; (ii) muscle tone abnormalities; (iii) hyperexcitable neonatal reflexes; (iv) variety of neurobehavior manifestations; (v) speech and language abnormalities; and (vi) evolving array of central processing abnormalities, such as sensorineural audiology and visuomotor dysfunctions. Concerns remain that the most vulnerable infants are likely to acquire BIND, either because their exposure to bilirubin is not identified as severe enough to need treatment or is prolonged but slightly below current threshold levels for intervention. Knowing that a total serum/plasma bilirubin (TB) level is not the most precise indicator of neurotoxicity, the role of expanded biomarkers or a "bilirubin panel" has yet to be validated in prospective studies. Future studies that correlate early "toxic" bilirubin exposure to long-term academic potential of children are needed to explore new insights into bilirubin's effect on the structural and functional maturation of an infant's neural network topology.

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1. Introduction

The syndrome of bilirubin-induced neurologic dysfunction (BIND) is severe and irreversible and/or with apparently transient post-icteric clinical sequelae. It occurs when total serum/plasma bilirubin (TB) levels exceed an infant's neuroprotective defenses (Table 1), resulting in neuronal injury in the basal ganglia, central and peripheral auditory and visual pathways, hippocampus, diencephalon, subthalamic nuclei, midbrain, cerebellum, and cerebellar vermis. Pontine nuclei, brainstem nuclei for oculomotor function, and respiratory, neurohumoral and electrolyte control are also affected [1,2]. The bilirubin dose–response relationship (severity of TB) to signs of neurotoxicity has been a subject of controversy and scrutiny [1,3–10] (Table 1). BIND was originally described by Johnson et al. from a uniquely focused Philadelphia single-center cohort in the "pre-phototherapy era" when babies were treated with exchange transfusion for TB levels considered worrisome or dangerous by then accepted treatment thresholds. In subsequent years, several investigators reported subtle manifestations in infants who had experienced bilirubin exposure of lesser degree than generally considered neurotoxic [12–18]. More recent studies have also suggested that more vulnerable preterm infants with modest TB levels sustain long-term neurodevelopmental impairment (NDI) at age 18–22 months [19–22]. In addition, even with treatment by exchange transfusion or phototherapy, term and late preterm infants with high TB levels and possible disordered albumin-binding may experience increased mortality and NDI associated with auditory neuropathic or visuomotor processing disorders that characterize BIND [23–25]. Conversely, many preterm infants are refractory to relatively high bilirubin loads in the absence of increased production rates, with optimal elimination of bilirubin and sufficient ability to bind bilirubin to albumin. Clinical neurologic signs range from being reversible to irreversible (Fig. 1). These are either single or multiple domains of: (i) neuromotor abnormalities; (ii) muscle tone abnormalities; (iii) hyperexcitable neonatal reflexes; (iv) range of neurobehavior manifestations; (v) speech and language abnormalities; (vi) and evolving array of recently described central processing abnormalities, such as sensorineural, audiological, and visuomotor dysfunctions.

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Table 1
Proposed definition of hyperbilirubinemia.

Total bilirubin levels	Percentile at age >72 to <120 h	Proposed use of adjective for severity
≥12.9 mg/dL (220 μmol/L)	≥40th percentile	Mild to moderate
≥17.0 mg/dL (291 μmol/L)	≥95th percentile	Moderate/significant
≥20.0 mg/dL (342 μmol/L)	≥99th percentile	Severe
≥25.0 mg/dL (428 μmol/L)	≥99.9th percentile	Extreme
≥30.0 mg/dL (513 μmol/L)	≥99.99th percentile	Hazardous

Confounding effects include: prematurity, hemolysis, perinatal–neonatal complications, altered bilirubin–albumin binding, severity and duration of bilirubin exposure, and individual vulnerability of the infant related to genetic, family, social, and educational predilection, regardless of the cause of the hyperbilirubinemia. Tools that better assess specific domains of multisensory processing disorders of BIND would allow for prospective surveillance of at-risk infants [14,23–27] and are often normal by physical exam at hospital discharge. Currently, clinical practice is governed by concerns for prevention of kernicterus rather than of BIND [28–31].

2. Background

2.1. Neuroanatomical vulnerability

Beyond the traditional recognized areas of fulminant injury to the globus pallidus in infants with kernicterus, other vulnerable areas include the cerebellum, hippocampus, and subthalamic nuclear bodies as well as certain cranial nerves. The increased neuromotor activity level in infants with BIND at age 18 months may be a reflection of minor dysfunction in these subcortical circuitries, especially in the networks of the basal ganglia and cerebellum. The hippocampus is also markedly affected by age-related morphological changes. It is generally assumed that a loss in hippocampal volume results in functional deficits that contribute to age-related cognitive decline. Lower gray matter volumes within limbic–striatal–thalamic circuitry are common to autism spectrum disorders and schizophrenia [32,33]. Unique features of each disorder include lower gray matter volume within the amygdala, caudate, frontal and medial gyri for schizophrenia, and putamen for autism. In terms of brain volumetrics, autism spectrum disorders and schizophrenia have a clear amount of overlap that may reflect shared etiological mechanisms. Possibly, in a similar manner, overlap with BIND that manifests a distinctive neuroanatomy raises the question about how these lesions occur in the context of common etiological pressures.

Table 2
Neonatal manifestations of bilirubin-induced neurologic dysfunction [40].

Outcomes	Hyperbilirubinemia TB 12.9–21.0 mg/dL (220–359 μmol/L)	Comparator TB < 11.7 mg/dL (200 μmol/L)	Adjusted ORs (95% CI)
No. of neonates	43	70	
Lethargy (neonatal)	30%	11%	3.7 (1.3–10.4)
Activity level (age, 18 months)[a]	4.7 ± 0.6	4.3 ± 0.6	0.31 (0.07–0.55)

TB, total bilirubin; OR, odds ratio; CI, confidence interval.
[a] The Toddler Behavior Assessment Questionnaire included assessment of activity level on a scale of 1–7 (see text for coding details).

2.2. Neuromotor dysfunction

The recently reported Dutch studies introduce categorization of minor neurologic dysfunctions that allows us objectively to gauge their clinical significance [8,34–38]. Age-specific Hempel's neurologic assessment examines five domains of function: fine motor, gross motor, posture and muscle tone, reflex, and visuomotor. Spectrums of dysfunction are categorized as “normal” (no dysfunction), “simple” (minor), “complex” (more than one domain), or “neurologically abnormal” [39]. Neurological well-being also needs to be adjusted by a child's age and social and educational backgrounds as well as prenatal and perinatal histories [36]. Lunsing et al. [40] have used these sensitive measures to assess neurodevelopmental outcomes and reported similar rates of minor neurologic dysfunction for hyperbilirubinemia defined as TB > 220 μmol/L (12.9 mg/dL) versus a control group (TB ≤ 220 μmol/L, 12.9 mg/dL) (Table 2). Their findings are consistent with the three previous reports indicating that moderate hyperbilirubinemia (TB > 220 μmol/L, 12.9 mg/dL) in healthy term infants does not affect neurological outcome [27,39,41]. However, when further parsed by TB > 300 μmol/L (>17.5 mg/dL), they demonstrated an increased risk of complex minor neurologic dysfunction (similar to the definition of BIND) (Table 3). The odds ratio (OR) for this observation was 4.2 [95% confidence interval (CI): 1.02–17.37]. As neonates, these hyperbilirubinemic babies were more often lethargic than controls (OR: 3.5; 95% CI: 1.3–9.5). More importantly, at age 18 months, the hyperbilirubinemic cohort as a whole had higher hyperactivity scores than the controls (effect: 0.32; 95% CI: 0.08–0.56).

2.3. Auditory dysfunction

Dysfunction in hearing is modulated by gestational age. De Vries et al. [12] reported that preterm infants with birth weight

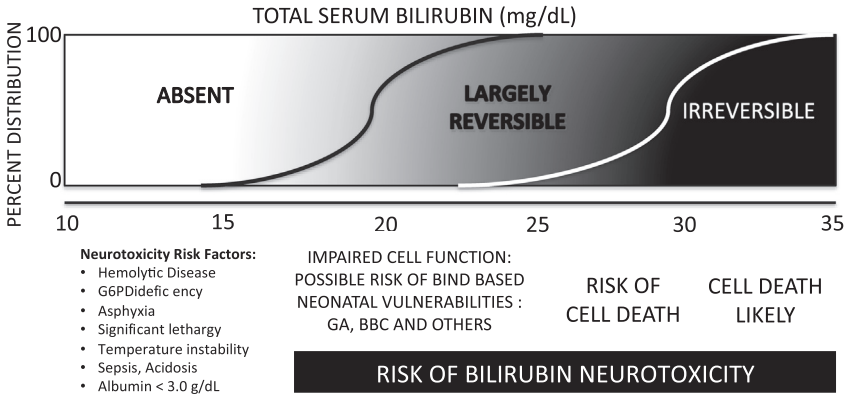

Fig. 1. Model for reversible bilirubin neurotoxicity (inspired by Bratlid [11]). G6P, glucose-6-phosphate dehydrogenase; GA, gestational age; BBC, bilirubin binding capacity.

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