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Early recognition of neonatal hyperbilirubinemia and its emergent management

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Summary Hyperbilirubinemia and kernicterus are re-emerging as prominent clinical concerns and have been hypothesized to be secondary to increased breast-feeding rates, early hospital discharges and overall lack of concern for the potential impact of severe hyperbilirubinemia on healthy term newborns. Although the clinical symptoms can be non-specific and vague, they could be early, insidious and heralding signs of acute bilirubin encephalopathy (ABE) or acute stage kernicterus. Because it is highly prevalent, evaluation of a jaundiced neonate requires detailed questions about specific signs, review of birth and postnatal histories, evaluation of predischarge data, and possibly an emergency clinical evaluation of the neurological status of the infant. Medical urgency to evaluate, investigate and monitor such a newborn ensues from the possibility of rapid progression that might lead to permanent sequelae of bilirubin-induced neurologic dysfunction (BIND). Early recognition of the urgency and rapid transition to treatment seem to be the major barriers leading to delay in therapy. However, because there is a well-established and relatively safe treatment for neonatal jaundice, there should be zero tolerance for kernicterus, and BIND prevention has become a national priority in the USA. This paper reviews the clinical signs and epidemiology of ABE and BIND and presents a system-based strategy for preventing their occurrence, focusing particularly on the transition from recognition of clinical jaundice to actual treatment. A novel emergency-room-based protocol is presented as an example of how to expedite and facilitate rapid progression to treatment.

Introduction

The majority of otherwise healthy newborns have clinical jaundice associated with increased concentration of total serum bilirubin (TSB). Although the outcome for the majority is benign, infants with untreated, extremely

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high TSB levels can develop signs of acute bilirubin encephalopathy (ABE). If not treated immediately, they might go on to develop kernicterus, a chronic, neurologically devastating condition resulting from bilirubin toxicity. The past focus has been on inpatient systems-based approaches that include detection of early-onset jaundice, predischarge assessment of risk for the development of subsequent hyperbilirubinemia, and early follow-up.[1–5] Ideally, these efforts would avoid delayed detection of excessive levels of TSB and limit the associated risk of neurologic injury, thus promoting a safe transition from the birth hospital to home.[6] However, recent changes in healthcare practices, including early discharge of newborns, have transformed the management of neonatal jaundice into an outpatient problem.[7,8] Despite its high prevalence in newborns, an elevated TSB concentration, because of its potential toxicity (especially when associated with signs of encephalopathy), is considered a neonatal emergency and must be addressed urgently.

Epidemiology: scope of the problem

More than 60% of otherwise healthy newborns develop hyperbilirubinemia during the first week of life, and most are discharged from their birth hospital before the usual peak of TSB (age 72–120 h). Hyperbilirubinemia typically resolves by 7–10 days of age and the outcome is usually benign. However, severe hyperbilirubinemia, defined as TSB above the 95th percentile for age in hours (high-risk zone), occurs in 8–9% of infants during the first week, with approximately 4% affected after 72 h.[9,10] Without appropriate intervention, progressive increase in hyperbilirubinemia to values >25 or 30 mg/dL (greater than 99th percentile for age in hours) places otherwise healthy babies at risk of bilirubin-related brain damage (kernicterus). The precise incidence of extremely high levels of hyperbilirubinemia and bilirubin neurotoxicity is not known because routine surveillance has been unavailable. Although, in a preliminary report, 82 cases of kernicterus were identified in New Jersey from 1992 to 2001, resulting in an estimated rate of 7.5 cases per 100,000 live births, the estimated incidence is about 1 in 30,000 infants discharged from well baby nurseries[2] (Table 1).

Pathophysiology

Unconjugated bilirubin is fat soluble; it crosses cell membranes and is potentially neurotoxic. However, toxicity is generally avoided because most unconjugated bilirubin is bound to albumin. Hyperbilirubinemia develops when the rate of bilirubin production via the breakdown of heme by the reticuloendothelial system exceeds the rate of elimination, primarily by conjugation. Various genetic, environmental, and racial factors affect the equilibrium between these processes. For example, albumin binding capacity is reduced by acidosis, immaturity, and competitive binding of substances such as salicylates, sulfonamides, and free fatty acids.

From a management perspective, it is useful to categorize severe hyperbilirubinemia according to its time of onset, early or late, regardless of its specific etiology (Fig. 1). In general, early-onset severe hyperbilirubinemia is associated with increased bilirubin production, while late-onset hyperbilirubinemia is often associated with delayed bilirubin elimination with or without increased bilirubin production.[11–13]

Early-onset hyperbilirubinemia (TSB values >75th percentile prior to 72 h of age) is a high-risk condition because it often presents with an acute and rapid rise in TSB values, which might reach levels above the 95th percentile within the first 12 h of life. Affected infants are typically identified by visual recognition of jaundice by nurses and subsequent testing of transcutaneous or serum bilirubin concentration. The etiology in the majority of these cases is hemolysis from ABO incompatibility, although this might not always be confirmed.[2,11,12]

Although early-onset hyperbilirubinemia might be identified at the birth hospital, depending on the timing of hospital discharge, both early and late onset hyperbilirubinemia can occur at home. Late-onset hyperbilirubinemia (TSB values >95th percentile after 72 h of age) can usually be predicted by predischarge bilirubin screening.[4] Late-onset hyperbilirubinemia often results from decreased bilirubin elimination. Inadequate breast-feeding with consequent dehydration and increased enterohepatic circulation of bilirubin is frequently a contributing factor. Other risk factors include familial or ethnic risk factors (siblings with jaundice, east Asian or Mediterranean descent, Gilbert's syndrome, and as yet unrecognized genetic polymorphisms of the glucoronyl transferase gene). Of note, glucose 6-phospho-dehydrogenase (G6PD) deficiency might be present in as many as 12.8% of African–American males.[14]

Acute bilirubin encephalopathy

The initial neurotoxicity of extremely elevated bilirubin levels results in acute bilirubin encephalopathy (ABE), which might progress to chronic conditions, including kernicterus. There is no evidence that neurotoxicity occurs at a specific bilirubin concentration. The critical level in

Table 1 Incidence of severe hyperbilirubinemia in term and near-term infants

Severe hyperbilirubinemia		Incidence	
TSB level >95th percentile	>17 mg/dL	8.1–10%	1 in 9
TSB level >98th percentile	TSB level >20 mg/dL	1–2%	1 in 50
TSB level >99.9th percentile	TSB level >25 mg/dL	0.16%	1 in 700
TSB level >99.99th percentile	TSB level >30 mg/dL	0–0.032%	1 in 10,000

Adapted from Bhutani et al.[11] based on the following references.[52–56]