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Hyperbilirubinemia, hemolysis, and increased bilirubin neurotoxicity

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ABSTRACT

Increased hemolysis in the presence of severe neonatal hyperbilirubinemia appears to augment the risk of bilirubin neurotoxicity. The mechanism of this intensifying effect is uncertain. In direct antiglobulin titer (DAT) positive, isoimmune hemolytic disease, the bilirubin threshold at which neurotoxicity occurs appears to be lower than in DAT-negative hyperbilirubinemia. In other hemolytic conditions, the hemolysis may simply facilitate the development of extremely high serum bilirubin levels. Whether the hemolytic process *per se* exerts an independent effect or whether a very rapid rise in serum bilirubin might lead to greater penetration of the blood–brain barrier is unclear. In this review, we survey the synergistic role of hemolysis associated with severe hyperbilirubinemia in the potentiation of bilirubin-induced neurotoxicity and suggest methods of identifying at-risk babies with increased hemolysis to allow for their increased surveillance.

Neonatal jaundice is a commonly occurring condition, visible icterus being noted in >80% of otherwise healthy neonates born at ≥35 weeks' gestation.[1,2] Usually the jaundice resolves spontaneously and causes no harm to the majority of infants. In some babies, hyperbilirubinemia can develop, which, if untreated, may become extreme. In this latter small subset, acute bilirubin encephalopathy, with the potential of progressing to the chronic athetoid form of cerebral palsy, known as kernicterus, may occur.[3,4] Kernicterus is relatively common in developing countries but also continues to be seen today in the industrialized world in which medical systems are well established and functional.[5,6] We therefore need to be able to identify the small group of infants who may go on to develop extreme hyperbilirubinemia and bilirubin encephalopathy.

Bilirubin production and elimination

Serum total bilirubin (STB) = bilirubin production − bilirubin elimination

At any point in time, the STB value represents the equilibrium between several concurrent processes involved in the production and metabolism of bilirubin. Bilirubin production results from heme catabolism, a process controlled by the

Abbreviations: AAP, American Academy of Pediatrics; COHb, carboxyhemoglobin; COHbc, COHb corrected for ambient CO; ETCO, end tidal carbon monoxide; ETCOc, ETCO corrected for ambient CO; G-6-PD, glucose-6-phosphate dehydrogenase; STB, serum total bilirubin; UGT, uridine diphosphate glucuronosyltransferase

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enzyme heme-oxygenase, and the resultant biliverdin is subsequently metabolized to bilirubin. Bilirubin elimination involves a sequence including uptake of bilirubin into the hepatocyte, conjugation by means of the enzyme UDP-glucuronosyltransferase 1A1 (UGT1A1), and then excretion of the newly formed conjugated bilirubin into the bile and the bowel. In newborns, a third process is in effect, the enterohepatic circulation. By means of the enzyme β-glucuronidase, the conjugated bilirubin reverts to its unconjugated form and is reabsorbed, rejoining the hepatic bilirubin pool via the portal circulation to again be eliminated. Depending upon the balance between these opposing metabolic pathways, the STB may remain stable, decrease, or rise.

Hyperbilirubinemia: The result of lack of equilibrium between bilirubin production and elimination

Hyperbilirubinemia is the result of an imbalance between bilirubin production and excretion. Using an index derived from blood carboxyhemoglobin, corrected for ambient carbon monoxide (COHbc), an accurate indicator of heme catabolism, and the serum total conjugated bilirubin expressed as a percentage of the total bilirubin (TCB%), reflective of bilirubin conjugation, Kaplan et al.[7] demonstrated the concept of bilirubin production and elimination imbalance mathematically. The STB correlated with both COHbc and TCB% individually. However, the ratio COHbc/TCB(%), representative of the combined forces of bilirubin production and conjugation, was better correlated with the STB, than was either of the individual correlation values. It was thus clearly demonstrated that lack of equilibrium between these processes, rather than each process in and of itself, was cardinal to the STB concentration.

Increased bilirubin production: The major modulating force

The formula, "Serum Total Bilirubin = Bilirubin Production − Bilirubin Elimination" characterizes, in the main, the relationships involved in estimating whether hyperbilirubinemia is due to an increased bilirubin production or diminished elimination, primarily conjugation. Because the enzyme activity of UGT1A1 in the newborn is only 1% or less of the activity in the adult,[8] the conjugation process can be regarded as the "bottleneck" of bilirubin elimination, and it can be assumed that almost all newborn infants have a significant degree of bilirubin conjugation immaturity. Taking the above-mentioned formula into account, if diminished bilirubin conjugation is universal, it is likely that increased bilirubin production plays the major and cardinal role in modulating the pathophysiology of neonatal hyperbilirubinemia.[9,10] As disorders affecting bilirubin conjugation are rarer than those resulting in increased heme catabolism, Stevenson et al.[9] emphasize that increased bilirubin production is most often the predominating factor causing the imbalance between the production and elimination processes.

Hemolysis: A major risk factor for severe hyperbilirubinemia

The 2004 American Academy of Pediatrics (AAP) guidelines for the management of hyperbilirubinemia[11] and the 2009 update[12] emphasize the role of hemolysis as a risk factor for hyperbilirubinemia and neurotoxicity and stress the need to identify hemolyzing newborns when managing neonatal hyperbilirubinemia. A hemolytic cause of jaundice is likely if the predischarge STB or TcB level is in the high-risk zone on the hour-specific bilirubin nomogram[13] or if jaundice is observed in the first 24 hours. Some important causes of hemolysis include isoimmune hemolytic disease [blood group incompatibility with a positive direct antiglobulin test (DAT), also known as the direct Coombs' test], glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, and hereditary spherocytosis. Unfortunately, because of overlap in results between hemolytic and non-hemolytic conditions in the newborn, the standard laboratory tests for hemolysis, such as the DAT, complete blood count including differential and smear for red cell morphology, and reticulocyte count are frequently unhelpful in the determination of hemolysis. End tidal carbon monoxide (ETCO) testing is based on the equimolecular production of CO and biliverdin for each molecule of heme catablolized.[14] This technique is able to confirm the presence or absence of hemolysis, and its measurement is the only clinical test able to provide direct reflection of the rate of heme catabolism and hence bilirubin production. Unfortunately, an apparatus required for this measurement, which was available at the time of writing of the AAP statement, was subsequently withdrawn from the market. A new instrument is currently being tested and prepared for marketing.

Severe hyperbilirubinemia, hemolysis, and bilirubin neurotoxicity

Hemolysis is a major risk factor for the development of hyperbilirubinemia, but is it also a potentiator of bilirubin neurotoxicity? Categorizing hemolytic conditions as "neurotoxicity risk factors" implies an increased risk of brain damage at equivalent concentrations of STB in an infant whose hyperbilirubinemia is the result of hemolytic disease compared with non-hemolytic etiologies. This is the reason why phototherapy and exchange transfusion are recommended at a lower STB level when any of the neurotoxicity risk factors are present.[11,12]

The first correlation between increasing STB concentrations and the risk of bilirubin encephalopathy and the concept that kernicterus was unlikely to occur in term infants unless the STB exceeded 20 mg/dL was reported by Hsia et al. in newborns with the paradigm of hemolytic conditions, Rh isoimmunization. In these infants, kernicterus was detected in 8% who had serum bilirubin concentrations of 19–24 mg/dL, 33% of those with concentrations 25–29 mg/dL, and 73% of those in whom the STB reached 30–40 mg/dL.[15] Although Rh disease has been virtually eliminated in industrialized countries with effective preventive medical systems, Rh isoimmunization continues to contribute to the etiology of kernicterus in developing countries.[16,17] In the early 1960s, kernicterus was first reported from Greece in association with another hemolytic condition, G-6-PD deficiency,[18] and G-6-PD deficiency remains an important cause of severe