

# All is not well: The Continual Challenges of Bilirubin Encephalopathy

Can. J. Neurol. Sci. 2005; 32: 273-274

The impression that kernicterus has virtually “become extinct” with the near elimination of Rh disease is incorrect. In fact, this neurological condition is experiencing a re-emergence, likely due to earlier hospital discharge and a “more lax” approach to the treatment of neonatal hyperbilirubinemia.<sup>1</sup> Up to one in 700 healthy term newborns may be at risk of kernicterus due to severe hyperbilirubinemia, as defined by total serum bilirubin greater than 250 mg/L or 428  $\mu\text{mol/L}$ .<sup>2</sup> Risk factors for hyperbilirubinemia include onset of jaundice within 24 hours of age, ABO and Rh incompatibility, or other hemolytic diseases such as glucose-6-phosphate dehydrogenase (G6PD) deficiency. Preterm or sick infants have increased susceptibility to bilirubin toxicity. In this issue, AIOtaibi et al<sup>3</sup> retrospectively reviewed the outcome of 12 neonates admitted to the Hospital for Sick Children with kernicterus over a ten-year period. The majority of cases (58%) were attributed to G6PD deficiency. Seven out of ten patients reportedly had abnormal neurodevelopmental outcome.

In neonates, serum bilirubin is comprised mainly of the unconjugated form, which is bound to albumin. When the blood binding capacity is exceeded, free unconjugated bilirubin then enters brain tissue and leads to neurotoxicity by a number of possible mechanisms. Bilirubin depletes cellular energy reserves by uncoupling oxidative phosphorylation and impairing mitochondrial function. Hyperbilirubinemia in a rodent model has also been shown to inhibit calcium and calmodulin-dependent protein kinase II, leading to alterations in both calcium-regulated ion conductance and neurotransmitter release, a situation which may lead to excitotoxic cell death.<sup>4</sup> Finally, in *in vitro* studies on rat neurons and astroglia, bilirubin was found to induce apoptosis and inhibit uptake of glutamate by astrocytes.<sup>5,6</sup> Thus, neuronal loss in bilirubin encephalopathy is due to both apoptosis and necrosis. Pathologically, the globus pallidus and subthalamic nuclei show neuronal loss, demyelination and gliosis. Other affected areas include the cerebellum, particularly Purkinje cells, and the CA2 region of the hippocampus. In the auditory system, central auditory pathways including cochlear nuclei, the superior olivary complex, nuclei of the lateral lemniscus and inferior colliculi are affected but the eighth nerve and inner ear structures are relatively spared.

Infants with acute bilirubin encephalopathy initially present with lethargy, hypotonia, and poor feeding. If hyperbilirubinemia is untreated, additional symptoms such as fever, seizures, high-pitched cry, retrocollis, and opisthotonus may develop. The classic tetrad of athetoid cerebral palsy, deafness, upward gaze palsy and dental enamel hypoplasia likely represents only the severe end of the clinical spectrum of brain injury resulting from chronic bilirubin encephalopathy. There is

now evidence that even modest degrees of hyperbilirubinemia might result in subtle brain injury, known as “bilirubin-induced neurologic dysfunction” or “BIND”.<sup>7</sup> Such patients may have variable degrees of cognitive, motor, or perceptual deficits. Isolated auditory neuropathy, central auditory processing defect, or movement disorders can occur in the absence of other classical signs of kernicterus.

Bilirubin encephalopathy should be considered in the differential diagnosis of children with non-progressive neurodevelopmental delay and a prior history of significant neonatal hyperbilirubinemia. The history should focus on both the duration and the peak serum bilirubin level, and identification of additional risk factors such as prematurity, sepsis, large cephalohematoma, fetomaternal blood group incompatibilities, and genetic disorders including Crigler-Najjar or Gilbert syndrome. Signs and symptoms of bilirubin encephalopathy in the newborn period such as seizures, abnormal tone, high-pitched cry, or opisthotonic posturing should be noted, and the presence of hearing loss, gaze palsy, dental enamel staining, spasticity, ataxia, athetosis, or dystonia on physical exam may help to confirm the diagnosis.

Two investigations that are particularly helpful in the diagnosis of bilirubin neurotoxicity are brain MRI and auditory evoked potentials combined with assessment of inner ear function. The MRI in kernicterus is distinct from hypoxic-ischemic injury as the globus pallidus is predominantly affected, with sparing of the striatum and cortex. The pattern of auditory dysfunction, known as “auditory neuropathy” is also distinct from most other causes of sensorineural hearing loss, in that there is absent or abnormal auditory brainstem response (ABR) with normal inner ear function, as assessed by otoacoustic emissions and cochlear microphonic responses. In the neonate, ABR may be completely absent, or may show abnormally increased interwave intervals I-III and I-V and decreased amplitude waves III and V. These ABR changes may improve or resolve with exchange transfusion. Electroencephalogram may be abnormal, but the findings are generally not specific for bilirubin encephalopathy.

As discussed by AIOtaibi et al,<sup>3</sup> bilirubin encephalopathy can be prevented through systematic assessment, close follow-up, and prompt intervention of newborns at risk for hyperbilirubinemia. The current recommendations emphasize the need to educate parents about neonatal jaundice, and to establish successful breastfeeding shortly after birth. As visual estimation of the degree of jaundice is unreliable, the levels of bilirubin should be correlated with the newborn’s postnatal age using established normograms. Pre-discharge identification of at risk infants and/or serum bilirubin measurement should be performed on all newborns, and infants who are discharged before 48 hours

of age will require close follow-up within the next 24 to 48 hours after discharge. Guidelines for bilirubin management should be followed, and severe hyperbilirubinemia is a medical emergency that requires immediate treatment with intensive phototherapy or exchange transfusion as necessary.<sup>8</sup>

*Jean K. Mah, Elaine Wirrell  
Calgary, Alberta*

#### REFERENCES

1. Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr* 2002;140:385-386.
2. Bhutani VK, Johnson LH. Urgent clinical need for accurate and precise bilirubin measurements in the United States to prevent kernicterus. *Clin Chem* 2004;50:477-480.
3. AlOtaibi SF, Blaser S, MacGregor DL. Neurological complications of kernicterus. *Can J Neurol Sci* 2005;32: 311-315.
4. Conlee JW, Shapiro SM, Churn SB. Expression of the alpha and beta subunits of Ca<sup>2+</sup>/calmodulin kinase II in the cerebellum of jaundiced Gunn rats during development: A quantitative light microscopic analysis. *Acta Neuropath (Berl)* 2000;99:393-401.
5. Rodrigues CMP, Sola S, Brites D. Bilirubin induces apoptosis via the mitochondrial pathway in developing rat brain neurons. *Hepatology* 2002;35:1186-1195.
6. Silva R, Mata LR, Gulbenkian S, et al. Inhibition of glutamate uptake by unconjugated bilirubin in cultured cortical rat astrocytes: Role of concentration and pH. *Biochem Biophys Res Commun* 1999;265:67-72.
7. Johnson L, Brown AK, Bhutani VK. BIND-A clinical score for bilirubin induced neurologic dysfunction in newborns. *Pediatrics* 1999;104:746-747.
8. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant. *Pediatrics* 2004;114:297-316.