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COMMENTARY

Just When You Thought It Was Safe. . .

Commentary on the article by Soorani-Lunsing *et al.* on page 701

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In this issue of *Pediatric Research*, Soorani-Lunsing *et al.* (1) present a provocative analysis of exposure or nonexposure to moderate degrees of hyperbilirubinemia in 20 healthy, nonhemolytic term infants and 20 control infants. In this very small study, the authors suggest that moderate hyperbilirubinemia was associated with a significant increase in minor neurologic dysfunction from infancy through the 1st year of life. The authors further report that a dose-response relationship between the degree of hyperbilirubinemia and severity of minor neurologic dysfunction was present.

Even though these infants were matched for sex and gestational age at birth with serum total bilirubin (STB) levels of 233 to 444 μM (13.6–25.9 mg/dL), their study population is confined to only healthy, nonhemolytic term newborns. Consequently, the majority of infants with pathologic jaundice associated with increased bilirubin production have been excluded. In addition, assessing hyperbilirubinemia only by STB levels does not provide a reliable estimate of bilirubin production, tissue bilirubin concentrations, or, most importantly, serum albumin-bound bilirubin concentrations. Albumin, the major binding protein for bilirubin, determines, for all practical purposes, the amount of bilirubin that remains in circulation. When bilirubin is produced at high rates, bilirubin will move out of circulation into tissue as the albumin binding capacity is approached and exceeded. Also, the rate of bilirubin distribution into tissue is dependent on other factors besides mass action, like pH. Bilirubin is a weak acid and decreases in pH are associated with increased translocation of free bilirubin from circulation into tissue. Thus, infants with increased bilirubin production as a cause of their jaundice and those with metabolic acidosis are likely to have increased tissue bilirubin for a given STB level.

Remarkably, the authors report a significant difference in minor neurologic dysfunction type 1 (the presence of hypotonia without significant reflex or postural deviancies) and minor neurologic dysfunction type 2 (mild abnormalities in muscle tone regulation in combinations with significant postural and reflux dysfunction) at 12 mo of age. They observed that the rate of minor neurologic dysfunction was greater overall in the study group (10 out of 20) than in the control group (2 out of 20), mainly due to a difference in the rate of type 2 dysfunction. The authors found that neurologic outcome was strongly related to the height of the STB peak. In fact, all five children with minor neurologic dysfunction type 2 had STB levels >335 μM (19.6 mg/dL). The authors also suggest that this height was related to the duration of the elevated STB level >340 μM (19.9 mg/dL). However, the size of this study population is far too small to definitively conclude that the height of peak STB is the most important factor in determining neurologic outcome and not the duration of this elevation. In a previous study by Seidman (2), STB levels >340 μM (20 mg/dL) had a measurable impact on cognitive performance at 17 y of age in male infants. The same male sex disadvantage is lurking in the Soorani-Lunsing study as well, although apparently found not significant by logistic regression analysis. However, in a later abstract by the same authors, no significant association between low intelligence scores and STB >290 μM (17 mg/dL) (3) was found, but these infants were treated with phototherapy when STB reached that level.

A few other issues regarding the analysis of this small number of patients are also concerning. The authors indicate that infants with "hemolytic disease" were excluded; however, specific data regarding blood type, Coombs' status, hematocrit, and reticulocyte count were, unfortunately, not presented. Subtle hemolysis, evident by one or more of these tests or by an indicator of bilirubin production such as end-tidal breath carbon monoxide, may therefore have been missed. The need to identify infants with hemolysis is exceedingly important as a longer duration of exposure to hyperbilirubinemia might be expected more often in the presence of hemolysis because of the greater bilirubin load and the limited hepatic conjugating capacity in most neonates. The cesarean section rate was also inexplicably much higher in the control group than in the study group. Although neurologic outcome was not apparently influenced by cesarean section, it is by no means clear what, if any, complicating factors led to hospital deliveries in the study group, given the fact that home deliveries are more prevalent in the Dutch system. Prenatal and perinatal risk factors, such as infection, or excessive bleeding suggesting abruption, certainly should be considered when assessing long-term neurologic and behavioral outcomes. Similarly, methodological considerations become paramount in studies focusing upon neurologic and behavioral outcome. An alarming rate of minor neurologic dysfunction was noted in the study group compared with the

control group in the neonatal period. However, the precise timing of the examination (sometime between 3 and 8 d) and whether any of the infants were under phototherapy at the time of examination is not reported. Masking of the individual performing neurologic assessments, although difficult in many situations, can be extremely important as well. In the present study, it could be argued that masking was almost impossible in the newborn period, but unfortunately, the examiner was reported to be "occasionally" aware of the group membership of the patients at the time of the 12-mo examination.

Nonetheless, the authors present potentially disturbing information. The follow-up study of these children, especially with respect to auditory processing, is extremely important, although the study period of 12 mo is certainly not sufficient time to evaluate the ultimate impact of hyperbilirubinemia on later learning in childhood. However, these investigators do echo the earlier observations of Newman and Klebanoff (4) and those of Grimmer and coworkers (5) that the presence of minor motor problems, such as mild hypotonia, awkwardness or nonspecific gait abnormalities at age 7 y, and a higher prevalence of choreiform dyskinesia at 5 to 15 y, should not be played down. In combination, the evidence suggests that moderate hyperbilirubinemia [233 to 444 μM (13.6 to −25.9 mg/dL)] may represent a measurable risk for development of minor neurologic dysfunction throughout the 1st year of life.

Furthermore, it is also worrisome that four of the five children with minor neurologic dysfunction type 2 received phototherapy. Thus, phototherapy may not guarantee protection against bilirubin toxicity when STB levels are high [>330 μM (19.6 mg/dL)] or when the duration of exposure is long. In addition, although this small study suggests that some infants with STB levels >340 μM (20 mg/dL) will escape without apparent neurologic consequence, this observation should not serve as reassurance to pediatricians about unsafe practice. There are no data to suggest that the relationship between STB levels and neurologic consequences is linear, yet there is the inclination to consider the risk of hyperbilirubinemia in this way.

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Bilirubin and Neurological Dysfunction—Do We Need To Change What We Are Doing?

Commentary on the article by Soorani-Lunsing *et al.* on page 701

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Soorani-Lunsing and coworkers prospectively evaluated 20 jaundiced infants whose total serum bilirubin (TSB) levels ranged from 233–444 μM/L (13.6–26 mg/dL) and compared them with a control group of 20 healthy, nonjaundiced infants matched for sex and gestation (1). All infants were ≥ 36 wk gestation. They examined the newborns between the ages of 3 and 8 d, at 3 mo (using a video recording), and at 12 mo for the presence of two types of minor neurologic dysfunction (MND). MND type I was defined as the "presence of hypotonia without significant reflex or postural deviancies"; type II MND refers to "minor abnormalities in muscle tone regulation in combination with significant postural and reflex dysfunction." At 1 y, 5/8 (63%) infants with bilirubin levels between 19.6–26 mg/dL (335–444 μM/L) had type II MND *versus* 0/20 control infants ($p < 0.001$). How do the results of this Dutch study compare with those of other studies and what we should do about them?

In a 4 year follow-up of 83 infants, Johnson and Boggs found abnormal neurologic examinations in 14/68 (21%) children whose indirect bilirubin TSB levels were ≥ 15 mg/dL (257 μM/L) *versus* 0/15 in those with TSB levels <15 mg/dL (2) (one tailed $p = 0.047$). Eleven of 14 had "minimal cerebral dysfunction" and 3 had other abnormal signs including fine and gross motor delay, athetoid movements and mild mental retardation. (It is not stated how many of the 3 infants had some or all of these findings.) In this study, however, 53% of the infants had hemolytic disease and 33% were premature and there is no mention of whether or not the follow-up evaluations were performed in a blinded fashion. In a more recent German study by Grimmer *et al.* (3) children at 7 y of age whose neonatal TSB levels had exceeded 20 mg/dL (342 μM/L), scored significantly worse on a scale designed to measure choreiform and athetoid movements (the choreiform dyskinesia scale). In that study 8/16 (50%) children in the hyperbilirubinemia group *versus* 3/18 (17%) in the control group had abnormal scores (data not found in the original paper but kindly provided by Dr. Grimmer).