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Hyperbilirubinemia and the Low-Birth-Weight Infant

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Bilirubinopathy, or kernicterus, was first described by Orth in 1875. The original descriptions of severe encephalopathy continued to appear through the early 1950s. It was assumed that kernicterus was, in the words of Vaughan, "always associated with erythroblastosis fetalis."[53] In 1953, Govan and Scott reported on ten cases of kernicterus without Rh incompatibility in infants at or about 32 weeks of gestation.[19] Unfortunately, the bilirubin levels were not reported for that population of infants. With the therapeutic revolution in Rh prophylaxis of the late 1960s and an equally dramatic change in support methods for infants with Rh incompatibility, kernicterus caused by that disorder is now rarely seen. Instead, the equally dramatic efforts aimed at the survival of the smallest infants, who are by definition "always ill," have uncovered an entirely different population at risk for the development of kernicterus.

Low-birth-weight infants (those weighing less than 2500 g and especially those below 1500 g) are now the predominant risk population on the basis of both autopsy specimens and experience with survivors. If the incidence of kernicterus is to be reduced, most efforts must now be directed toward this population, who would have the most to benefit from advances in our understanding of bilirubin metabolism, in the assay and binding properties of bilirubin, and in general improvements in management.

This review concentrates on the problems of bilirubin in relation to the low-birth-weight infant, the clinical manifestations of encephalopathy, and the biochemical basis of the disease process; it reviews briefly the tools available for assay of the population of infants at risk; and it attempts to describe the current management protocols for this population.

The incidence of kernicterus in the low-birth-weight population is very difficult to establish. In the late 1950s, a time when the aggressive management of hyperbilirubinemia in low-birth-weight infants was not considered to be particularly important, 32 of 85 low-birth-weight infants in a study by Harris and associates[22] died. Nine of those 32 had kernicterus, but only 1 had any clinical manifestations.

Stern and Doray reported on 23 infants with birth weights between 825 g and 2450 g and bilirubin levels ranging between 11.3 and 23.2 mg/dl.[47] Five of the infants in whom kernicterus developed had bilirubin levels of less than 15 mg/dl, but of 23 who were affected, 22 had associated findings such as acidosis, respiratory distress syndrome, and CO_2 retention. Eighteen of the 23 had had some evidence of hypothermia.

A more recent study of kernicterus, which compared 32 infants with kernicterus and 32 without, stated that the overall autopsy-proved incidence was approximately 5%.[50] Unfortunately, little information was provided on total protein or bilirubin-binding studies, but it was clear that clinical factors such as neurologic manifestations, temperature, treatment modalities, Apgar score, hematocrit, pH, PCO_2, PO_2, bilirubin, and sugar showed no correlation with the incidence of kernicterus. Kernicterus was seen more commonly in twins and in infants of older mothers. Infection did not seem to be a major concomitant of the disease. In Ackerman's study of kernicterus in low-birth-weight infants, the disease was found in 7 of 54 infants with birth weights of less than 1500 g.[1] Of those with bilirubin levels above 15 mg/dl, five of seven had kernicterus. The associated factor in this study was that of skin hemorrhage.

In a sequential study reported by Pearlman and co-workers, infants weighing less than 2250 g who were seen at postmortem examination showed a 64% incidence of kernicterus between the years of 1966 and 1967.[41] No cases of kernicterus were reported between 1971 and 1976. The peak bilirubin concentrations were notably higher for the earlier group than for the later group. The authors concluded that a vigorous approach to management with exchange transfusion and phototherapy had reduced the incidence of kernicterus substantially.

In our experience, the incidence of kernicterus was 11% in a postmortem population of 211 infants over a 7-year period (1974–1980); 19 infants weighed less than 1900 g.[43a]

CLINICAL MANIFESTATIONS

In 1961, Van Praagh described the clinical manifestations of kernicterus in three neonatal phases and one phase in older infants.[52] The first phase, which seemed to him entirely distinct, was characterized by hypotonia, lethargy, and diminished sucking. The second phase was characterized by spasticity and opisthotonos, along

with fever. The third phase was characterized by diminished spasticity. The last phase, seen in older children, included extrapyramidal signs, movement disorder, and deafness. These signs and symptoms were initially described in erythroblastotic infants of relatively large birth weight, and their appearance might be followed by death at any stage.

Some time later, it became clear that the manifestations of kernicterus in the newborn period among low-birth-weight infants was substantially different. Indeed, for these newborn infants there were few, if any, clinical manifestations among those who would ultimately survive the newborn period. For infants who died of their disease early in life, the primary clinical manifestations were respiratory distress and asphyxial injury. The postmortem findings were characteristic of kernicterus, including microscopic damage of neurons in the basal ganglion, the hippocampus and cerebellum, and the nuclei of the fourth ventricle.[29]

ROLE OF BILIRUBIN LEVELS

The clinical manifestations of kernicterus are now rarely seen among term infants and are assumed to be related to other diseases among preterm infants; likewise, the bilirubin levels alone have proved poor predictors of ultimate neurologic damage.

Older studies suggested that hyperbilirubinemia in preterm infants did not correlate with neurologic defects at 3 years of age unless the hyperbilirubinemia was associated with other complications of prematurity.[45] These studies and others suggested that it was not simply the relationship of the bilirubin level which was important but that additional factors might be involved. Wishingrad and associates, reviewing infants admitted for care between 1960 and 1963, revealed an incidence of kernicterus of 7 of 50 infants whose bilirubin level exceeded 18 mg/dl, and no kernicterus in infants whose bilirubin level remained at less than 15 mg/dl.[54] At that time, it was suggested that a conservative approach to exchange transfusion was perhaps justifiable, especially in view of the significant morbidity and mortality associated with that procedure. The authors further suggested that in premature infants without asphyxia, hypoproteinemia, or sepsis, exchange transfusion might not be needed until a bilirubin level of 24 mg/dl was reached. Later studies contradicted this early optimism and showed an increased incidence of hyperbilirubinemia and kernicterus among complicated cases of premature infants. Gartner and associates suggested that there was an association between intraventricular hemorrhage and kernicterus.[17] Other studies suggested that infection played a significant role.[40]

More recent studies suggest that risk factors cannot be used to determine which infants of similar birth weight are at risk for kernicterus. It has also become clear that peak bilirubin values are not substantially different in infants who do and in those who do not acquire kernicterus. Our own review suggests that among a large number of risk factors, percent weight loss in low-birth-weight infants and the male sex correlate with the incidence of kernicterus in postmortem specimens.[43a]

Clinical studies based on the classic portmortem findings may not be of help in separating the multiple factors associated with kernicterus. Although definitive evidence is lacking for a unique role of bilirubin in the high incidence of kernicterus among low-birth-weight infants, its well-recognized role in kernicterus among larger infants justifies aggressive treatment for the low-birth-weight infant with elevated levels of bilirubin. Ethical questions complicate any attempt at controlled trials with the use of any of the newer methods for measuring albumin–bilirubin binding or the concentration of free bilirubin.

PATHOPHYSIOLOGIC MECHANISMS OF BILIRUBIN ENCEPHALOPATHY

The mechanism by which bilirubin gains access to the central nervous system and either causes or contributes to central nervous system damage is not entirely understood. Early interest had centered about the absolute quantity of bilirubin in the serum. More recently, the fraction of free bilirubin not bound to albumin or to other secondary binding sites, the attendant effect of acidosis and asphyxia on the bilirubin–albumin relationship, and the effect of free bilirubin on oxidative mechanisms have claimed attention.

The basis for the causative role of bilirubin in the pathophysiology of the disease rests on Zetterström and Ernster's description of the effect *in vitro* of bilirubin on oxidative phosphorylation in mitochondrial preparations.[56] This has been confirmed by others.[13] The original clinical association of bilirubin in kernicterus derived from the observations of Hsia and co-workers.[24] Although it is possible that free bilirubin is simply attracted to cell destruction caused by other mechanisms that are as yet unclear, the effect on cell respiration may be the terminal event once bilirubin has gained access to the cells at risk. The tissue transfer of bilirubin from plasma to the central nervous system may be a reversible process, but the duration of the presence of bilirubin may have some effect on the central nervous system damage.

Karp suggested various mechanisms for the "selective toxicity of bilirubin for the neonatal brain," including immaturity of the blood–brain barrier and differences in lipid composition of the neonatal brain.[27]

Bilirubin is considered a lipophilic compound. It is essentially a polar molecule existing as a charged anion that associates with hydrogen. The establishment of intramolecular hydrogen bonds after folding of the molecule prevents water attachment, and the molecule becomes insoluble in water.[4] The four internal methyl groups give the weakly lipophilic characterization to the molecule. Toxicity is entirely dependent on this acid bilirubin form, which is insoluble in water and, because of its weak lipophilic character, may adhere to cell membranes. The lipid solubility of the free acid increases with polarity, and it is that form of the compound that penetrates the central nervous system.

Only unconjugated, free bilirubin that is unassociated with albumin or other binding sites is toxic to the central nervous system; this entity and the association of the bilirubin with albumin must be described in some detail.

Most bilirubin is albumin bound.[32] The binding is extraordinarily tight, more so than for most drugs and albumin. *In vitro*, a single mole of albumin binds up to two moles of bilirubin, but *in vivo*, with newborn albumin, the molar ratio is between 0.6 and 1 mole of bilirubin per mole of albumin.[31] This affinity is considerably reduced in sick, low-birth-weight infants.[26] In the presence of 3.5 g of albumin, it is possible that between 17.8 and 29.7 mg of bilirubin can be bound inasmuch as a molar ratio of 1 would permit binding of 8.5 mg per mole of albumin. Molar ratios well below 1 will reduce the binding capacity considerably. It is clear that the bilirubin–albumin binding ratio is even lower in low-birth-weight infants, but additional factors may be necessary for entry into the central nervous system.

It has been postulated that phosphocholine present in cell membranes may accelerate the deposition of bilirubin when the bilirubin–albumin molar ratio exceeds 0.7.[5] This phenomenon is augmented in the presence of acidosis, and it has been proposed that this mechanism occurs clinically. Nelson and associates studied the ability of bilirubin to kill cells with changes in pH.[35] They concluded that small changes in pH may be responsible for changes in albumin–bilirubin binding. More cells were killed at a pH of 7 than at 7.4 with constant amounts of bilirubin. These researchers further concluded that ionization and polarization of the bilirubin acid are augmented at low pH. The contribution of acidosis has been demonstrated in animal experiments. In monkeys, Lucey was unable to produce kernicterus with bilirubin infusion unless he also prepared the monkeys with asphyxia for 10 to 12 minutes during cesarean section.[33] Similar studies have been done in rabbits.[12]

The effects of drugs on the production of kernicterus were discovered initially by Silverman and co-workers in the 1950s.[16] Brodersen noted that sulfonamide in that well-known clinical misadventure did not force bilirubin from albumin binding sites; the drug simply occupied vacant sites and limited the capacity of albumin to carry and render innocuous additional quantities of bilirubin.[6] Fortunately, many of the most important drugs used in the early newborn, such as digitalis and diuretics, do not cause any substantial degree of competition for albumin binding. Some analgesics are known to be competitors, but the most potent competitor of all is radiographic dye used for cholangiography. Unfortunately, some of the preservatives used in commercially available albumins, such as sodium octanoate and acetyltryptophan, may occupy considerable numbers of albumin binding sites. Dicumarol is also noted to displace bilirubin from albumin.

Long-chain fatty acids are known to displace bilirubin when the concentration of fatty acids is four times the molecular concentration of albumin, but the effect of endogenously produced fatty acids on the bilirubin–albumin binding ratio of small premature infants is probably negligible. The newborn premature infant is certainly limited in the amount of fatty acids he can produce endogenously, and the exogenous administration of fatty acids must be tempered with a knowledge of the bilirubin levels.

Bilirubin bound to albumin is nontoxic, and there is usually a generous surplus of available binding sites. However, small amounts of bilirubin (less than

0.1%) are free, well below the calculated total binding capacity for a given level of albumin. In addition, bilirubin is known to bind to globulins, red blood cells, mitochondria, and platelets.[31]

Most therapeutic endeavors are aimed at preventing free bilirubin from gaining access to the central nervous system cells, reducing total levels of bilirubin, and improving bilirubin–albumin binding. Therefore, interest has developed in the measurement of albumin–bilirubin binding capacity and of free bilirubin in the system.

METHODS OF BILIRUBIN ASSESSMENT

The amount of bilirubin acid molecules present in the serum at any one time is exceedingly small. Since a dynamic equilibrium exists between various binding sites and bilirubin, it is not expected that assessment of free bilirubin will be clinically useful in predicting which infants are at risk for kernicterus. Strictly speaking, of course, the affinity of bilirubin for nonspecific sites on erythrocytes, platelets, collagen, or fat or for secondary sites on the albumin molecule greatly affects the capacity of the system to absorb additional bilirubin. Although the fact is not generally appreciated, these sites may have a substantial effect on the ability of bilirubin to enter central nervous system tissue. Even the bilirubin that is considered free and unbound may not be free enough from secondary binding sites to present any immediate danger to the central nervous system. For all these reasons, less effort has been made to develop assay techniques for unbound bilirubin. It is far more useful to estimate the capacity of the bilirubin–albumin binding system to absorb additional quantities of bilirubin, and various methods have been developed for this purpose.

More than 20 different techniques of bilirubin assessment have been described, some of them cumbersome and nonreproducible. None have been subjected to long-term controlled studies to assess their efficacy, although there are some anecdotal data that suggest they may have some benefit. Some clinical data exist for phenolsulfonphthalein (PSP) binding capacity, hydroxybenzeneazobenzoic acid reserve binding capacity, Sephadex column chromatography, and peroxidase assay. However, the attempt to discover a specific and safe binding capacity for low-birth-weight infants has not been successful. Most promising among the most recent techniques is spectrofluorometry; the fact that it requires little blood and can be done rapidly in a semiautomated fashion is its chief virtue.[10,30] Our laboratory is in the process of evaluating this technique, but it cannot yet be recommended as a basis for clinical decisions. A full and complete discussion of these techniques is available.[21,54]

Currently, none of the methods available has met the definitive tests of reliability, reproducibility, and rapidity. Although several studies suggest that high levels of albumin–bilirubin saturation sites are probably hazardous, there is as yet no conclusive information.[9,18,37,44] Substantial ethical questions need to be faced in the creation of study protocols based on bilirubin–albumin assay if controlled

studies are to provide definitive information on safe and unsafe bilirubin–albumin binding levels.

MANAGEMENT

The management of the low-birth-weight infant with hyperbilirubinemia involves some degree of prophylactic care before and after delivery. Recently, there have been significant improvements in techniques that delay early labor by the use of β-sympathomimetic agents, however, all prematurity cannot be prevented. It is to the infant's advantage, if he must be born prematurely, to be born with a minimum of trauma and insult from asphyxia. Trauma to a frail, friable vascular system can only lead to hemorrhage, which will ultimately result in hyperbilirubinemia through increased breakdown of red blood cells. Advocates of selective cesarean section for very small premature infants have demonstrated diminished mortality and morbidity for the low-birth-weight infant. Asphyxia may adversely affect liver function, reduce sugar stores by anaerobic metabolism, and affect the blood–brain barrier, which excludes bilirubin from the central nervous system. Prevention of hyperbilirubinemia and its complications may contribute toward improved results.

Careful attention to fluid balance in the exposed low-birth-weight infant is essential. Data from our institution in an autopsy population suggest that excessive weight loss in the immediate newborn period correlates more often than any other single variable with the incidence of kernicterus. In these studies, the commonly accepted factors such as respiratory distress syndrome, anoxia, acidosis, hypoglycemia, hypernatremia, and intracerebral hemorrhage showed no significant association with the development of kernicterus. Although it is exceedingly difficult to compare the extent of asphyxia and acidosis in study populations of sick infants, it would seem prudent to avoid these additional stresses whenever possible.[43b]

We have used phototherapy very little in the management of hyperbilirubinemia of appropriately grown, term-weight infants and have reserved its use for those with bilirubin levels of more than 15 mg/dl, but we have employed phototherapy at very much lower bilirubin levels for low-birth-weight infants and have used it prophylactically in all low-birth-weight infants weighing less than 1500 g.

The mechanism whereby fluorescent light induces a reduction in serum concentration of bilirubin is not entirely understood. It is assumed that bilirubin undergoes photooxidation in the skin, but it is also known that increasing amounts of unconjugated bilirubin appear in the bile of experimental animals such as Gunn rats after radiation with light.[39] The real key to the effect of light on bilirubin *in vivo* may be related to a light-induced change in stoichiometry produced by the radiation of the bilirubin molecule.[15] This change occurs in the intramolecular hydrogen bonding within the molecule and renders the bilirubin molecule more water soluble. Theoretical concerns have been raised that the oxidation of albu-

min produces a diminution in albumin-binding affinity.[36] In addition, some authors have been concerned about the possible diminution or alteration of serum albumin as a consequence of phototherapy.[14,55] However, the decrease in total bilirubin concentration noted during phototherapy more than compensates for these other effects.[55]

Numerous authors have used phototherapy successfully for the management of low-birth-weight infants, but by no means has kernicterus been avoided in all instances, and there are case reports in which kernicterus has occurred despite the use of phototherapy.[23,28,41,48] Water loss with phototherapy has been extensively reviewed by a number of authors; it seems there is an increase in both stool water loss and insensible water loss with phototherapy.[38] These factors must be recognized when managing a low-birth-weight infant who may already have high insensible water losses.

Several authors have suggested that phenobarbital given to mothers before delivery might have a beneficial effect on the capacity of the liver to conjugate and excrete bilirubin.[8,15,23,38,49,51] It appears that 100 mg of phenobarbital taken at night for the last several weeks before delivery has no adverse effect on fetus or mother, but that it does diminish the incidence of hyperbilirubinemia at levels above 16 mg/dl in a population of term infants. Phenobarbital given directly to premature infants of less than 36 weeks of gestation produced lower bilirubin levels in a study population as compared with controls, but the numbers were extremely small in both groups.[38]

The rapid breakdown of red blood cells in low-birth-weight infants also contributes to the increase in bilirubin. Gross suggested the administration of vitamin E, an antioxidant, to deficient low-birth-weight infants to reduce the bilirubin levels.[20]

The ultimate defense in the management of hyperbilirubinemia remains exchange transfusion based on some arbitrary serum bilirubin level. The procedure of exchange itself is associated with a mortality as high as 5% in this population of infants at risk.[21] The complications of the procedure have been well described and include hypoglycemia, electrolyte abnormalities, acid–base abnormalities, thrombocytopenia, hemodynamic instability, and, most ominously, changes in intracranial pressure.[2,3,7,16,25,42,43]

Although designation of an absolute bilirubin level as an indication for exchange transfusion is impossible, there are suggestions for exchange levels on the basis of clinical and laboratory experience. The 1% method suggests that exchange transfusion be done when the infant's birth weight in grams corresponds to the milligrams of bilirubin per deciliter.[21] A second method uses a graded scale: for infants of birth weights less than 1250 g, the level would be 10 mg/dl; for infants between 1250 g and 1500 g, a peak level of 13 mg/dl; and for infants between 1500 g and 1999 g, a level of 15 mg/dl.[31]

In our experience, a linear regression curve of weight *versus* bilirubin in infants with autopsy-proved kernicterus suggests the need for exchange transfusion substantially below the 1% level.[43a] We also found infants weighing more than 1900 g with autopsy-proved kernicterus who had bilirubin levels far below the

1% level. In these infants there was no difference in the incidence of acidosis, asphyxia, hypoxemia, or any of the other suggested factors that predispose toward the development of the disease. Significant numbers of the control infants, similar in all other respects, who died without kernicterus had bilirubin levels above the 1% level, and it would be necessary to perform exchange transfusions on a large number of infants in order to protect a very few. We have no long-term follow-up data on the survivors, and it is possible that a policy of early exchange transfusions may have prevented damage in a survival population as compared with those in these postmortem studies, but it appears once again that no level of bilirubin in a preterm infant is particularly reassuring or safe under all circumstances.

The technique of exchange transfusion is generally successful in lowering bilirubin concentration. But because of rapid equilibration, levels return to 60% of original within 30 minutes.[34] Heparinized blood and blood treated with acid citrate dextrose (ACD) or citrate phosphate dextrose (CPD) have been used successfully for exchange transfusion. Heparinized blood has the advantage of causing no changes in pH or calcium, but it is theoretically possible that it mobilizes free fatty acids, which may compete with a residual bilirubin for albumin binding sites.[31] CPD- and ACD-treated blood requires buffering for the acid load imposed. It is generally desirable to use THAM (tromethamine) for the procedure, to raise the pH to between 7 and 7.1. Pretreatment with albumin has produced conflicting results.[11]

The management of an individual infant with hyperbilirubin, therefore, must remain for the time being in that most unsatisfactory ground between clinical judgment and blind luck.

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