Hyperalimentation Associated Hepatotoxicity in the Newborn*

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ABSTRACT

Total parenteral nutrition (TPN) has become a mainstay of modern neonatal care for the increasing population of premature infants who survive their initial pulmonary disease. As with other advances in neonatal therapy, hyperalimentation has associated complications and limitations, primary among them its toxicity to the liver. The basic pathologic lesion is bile cholestasis which is probably multifactorial in etiology. Amino acid solutions, excessive calorie-to-nitrogen ratios, and deficient trace elements and antioxidants have all been implicated in this process. Total parenteral nutrition-cholestasis can progress to portal fibrosis and irreversible cirrhosis if long-term hyperalimentation is required. Most at-risk for this iatrogenic condition are those premature infants less than 1500 g birth weight who are exposed to TPN for longer than two weeks. Enteral feedings providing as little as 10 percent of caloric intake are beneficial, and the prognosis for recovery is good once enteral feedings are established.

History

In 1968, Wilmore and Dudrick first reported the successful long-term use of total parenteral nutrition (TPN) in an infant at the Children’s Hospital of Philadelphia.11,29 This was followed in 1969 by Filler et al13 with a case series of 14 infants managed with TPN at the Children’s Hospital in Boston. The infants involved primarily had surgical complications of the gastrointestinal tract for which they could not be fed. The successful implementation of intravenous hyperalimentation with dextrose, amino acids, and fat represented a major advance in neonatal care and survival. Thus began the inclusion of hyperalimentation in the armamentarium of pediatric care, initially for post-surgical patients. Its use quickly extended, however, to the increasing numbers of premature infants who were surviving the pulmonary diseases of prematurity to require intravenous nutritional support until able to tolerate full enteral feeds.

Then, in 1971, came a case report by Peden and his associates Witzleben and Skelton,20 of cholestasis and cirrhosis on post-mortem exam in a premature infant.
after long-term TPN. This marked the beginning of the recognition of hyperalimentation-related hepatotoxicity and the first step in defining its pathophysiology and mechanisms. A series of case reports then quickly appeared confirming the association between hyperalimentation and cholestatic liver dysfunction.\textsuperscript{3,4,22} As had happened before with advances in neonatal care, a milestone in supportive care of the premature was followed by the recognition of its toxicity. Just as retrolental fibroplasia and blindness resulted from the unmonitored and excessive use of supplemental oxygen and bronchopulmonary dysplasia was seen with the widespread use of mechanical ventilation in neonates, so hyperalimentation revealed its limitations.

**Clinical Features**

Twenty years of experience with hyperalimentation in the neonatal intensive care setting have demonstrated that the premature infant less than 1500 g, and usually 25 to 32 weeks gestational age, is most likely to develop TPN hepatotoxicity, especially if the duration of hyperalimentation is greater than two weeks.\textsuperscript{21} With current survival rates, the population at risk is considerable. During a nine month period at the Hospital of the University of Pennsylvania, for example, in which 2613 live births occurred, 34 newborns less than 1500 g were admitted to the Neonatal Intensive Care Unit who subsequently received a minimum of 14 days of TPN, thus making them potential candidates for hyperalimentation hepatotoxicity. In a series of 62 infants reported by Beale et al.,\textsuperscript{2} 50 percent of neonates with a birth weight less than 1000 g, and 18 percent of those 1000 to 1500 g in weight developed cholestasis. Of infants weighing 1500 to 2000 g at birth, only seven percent developed cholestasis.

Clinically, the hepatotoxicity associated with hyperalimentation in the newborn is insidious in onset; the patients asymptomatic. Hyperbilirubinemia is the first abnormality detected, typically three to four weeks after initiation of TPN and beyond the usual seven to 10 day postnatal peak of unconjugated, physiologic hyperbilirubinemia. Biochemically, however, elevated serum bile and concentrations appear as early as five days\textsuperscript{6} after hyperalimentation is started and are present in 85 percent of infants after two weeks of TPN.\textsuperscript{24} Following the rise in serum bile acids, the most detectable biochemical event is an increase in serum conjugated bilirubin. Serum aminotransferases are frequently normal early in the course of TPN-associated hepatotoxicity and only increase after several weeks of cholestasis.

Alkaline phosphatase concentrations are not particularly helpful in the diagnosis in the newborn period because of the normally high levels and the high concurrent incidence of bone disease in pre-matures. Gamma peptidyl transferase, while a sensitive indicator of hepatic dysfunction, is not specific for TPN-associated hepatotoxicity and is elevated by drug therapy, particularly anti-convulsants. 5'-Nucleotidase is a useful indicator of hepatic dysfunction during parenteral nutrition. Hepatic synthetic function, reflected in serum albumin and pre-albumin concentrations, and prothrombin time remains normal with hyperalimentation-associated liver disease.

**Evaluation of Patients with Suspected TPN Cholestasis**

Hyperalimentation-associated cholestasis is a diagnosis of exclusion. The evaluation of patients with suspected TPN cholestasis thus involves ruling out the various other causes of cholestatic liver disease in the newborn. An ultra-
sound of the biliary tract is a noninvasive study useful to detect structural abnormalities such as cysts and gallstones, and to detect the presence or absence of a gallbladder. Blood can be screened for alpha-1-antitrypsin phenotype, alpha-1-antitrypsin deficiency being a leading cause of neonatal cholestasis. Urine and serum samples can also be sent for amino acid analysis to look for evidence of metabolic disorders, especially tyrosinemia and galactosemia. Cystic fibrosis should be considered and excluded as a cause of neonatal cholestasis. A sweat chloride test for cystic fibrosis is difficult to accomplish in the premature infant, however, owing to inadequate sweat collection. Urinary tract infection can result in cholestasis and can be diagnosed on the basis of urine chemtest and culture. Intrauterine-acquired infections, such as the TORCH group, should be considered, particularly in the neonate who is small-for-gestational age and/or dysmorphic. These include, Toxoplasmosis, Other, (syphilis, parvovirus, HIV), Rubella, Cytomegalovirus, and Herpes. To rule out biliary atresia, radioisotope scans (HIDA, PIPIDA) use an iminodiacetic acid agent to demonstrate hepatocyte function by the ability to excrete the isotope into the GI tract. Finally, liver biopsy may be necessary to document both etiology and extent of hepatotoxicity. In one series of 47 newborns evaluated for TPN-associated cholestasis, five (10 percent) were found to have disorders other than hyperalimentation as the cause for their cholestasis.

Pathology—Liver Biopsy

The initial lesion seen on liver biopsy and a constant feature of hyperalimentation-associated hepatotoxicity is bile stasis, both canalicular and hepatocellular. Cohen and Olsen identified canalicular cholestasis in 84 percent of newborns after as little as 10 days on hyperalimentation, followed by bile duct proliferation in 64 percent after three weeks of TPN. Next, there is a ballooning of hepatocytes and Kupffer cell hyperplasia, leading to lobular disarray of liver structure. Deposits of lipofuscin pigment are present in the Kupffer cells and accumulate as parenteral nutrition continues. Mild-to-severe portal inflammation develops that is predominantly lymphocytic, although eosinophils may also be prominent. Finally, portal fibrosis appears. Fifty percent of infants reported by Dahms and Halpin had panlobular or pericellular fibrosis on initial liver biopsy. Irreversible changes such as moderate to severe portal fibrosis were seen only after 90 days of TPN and more advanced cirrhosis after even longer duration of TPN.

Pathophysiology

The pathogenesis of hyperalimentation-associated cholestasis is unknown, but appears to be multifactorial in etiology. It is important to remember that the neonates who are prone to this disorder are premature and often have significant lung disease, hypoxia, hemodynamic instability, and infections. In addition, they are repeatedly exposed to blood products which put them at risk for acquired hepatitis and other infections, and medications that affect liver function. There is an inherent immaturity of the enterohepatic circulation that contributes to bile stasis, resulting in a “physiologic” cholestasis. Thus, because of the lack of enteral feedings in many of these neonates, there is a lack of stimulation of enteric hormones such as secretin, glucagon, gastrin, and motilin, which play a role in the initiation and maintenance of normal bile flow. While each of the components of hyperalimentation solutions has been implicated in the development of hepatotoxicity, the evidence for amino
acid solution toxicity is the most convincing. Both clinical and laboratory studies have demonstrated the cholestatic potential of amino acids. Since cholestasis appears to be the primary hepatopathological lesion, amino acid solutions contribute to the earliest stage in the development of TPN hepatotoxicity. Deficiency states of carnitine, molybdenum, taurine, selenium, and vitamin E may also add to a predisposition to cholestasis with TPN. Specifically, carnitine deficiency has been associated with prolonged TPN, leading to inadequate fatty acid oxidation by impairment of transport across the mitochondrial membrane. Molybdenum is an ultratrace metal that is a co-factor in the enzyme system responsible for the degradation of sulfur-containing amino acids. Its deficiency may potentiate the hepatotoxicity of amino acid solutions. Taurine is an essential amino acid-like substance that neonates have only a limited ability to synthesize. Since taurine is involved in the conjugation of bile acids, it may be a rate-limiting factor in bile flow, in which case its deficiency could contribute to cholestasis. Selenium, another trace element, is involved in antioxidant defense, as is vitamin E, both of which are known to be deficient in premature infants.

Management of TPN-Associated Cholestasis

Those patients most at risk for TPN-associated hepatotoxicity are exactly the ones least able to tolerate its withdrawal once evidence of toxicity presents. In lieu of stopping hyperalimentation, certain modifications of its administration may attenuate its hepatotoxicity. Reducing the protein infusion to two g per kg per day is suggested to minimize amino acid-related damage while continuing to meet the nitrogen requirement in the growing premature. Intravenous fat emulsions should be continued since currently available preparations are not associated with hepatotoxicity. A calorie-to-nitrogen ratio of less than 200:250 is recommended as is the initiation of enteral feeds, if possible. The prognosis for TPN cholestasis is good, if enteral feeds can be started and maintained, even if they provide as little as 10 to 20 percent of total calorie intake. The worst clinical outcome has been reported for those infants unable to tolerate any enteral feeds. Although liver enzyme changes persist for weeks to months after TPN is discontinued, the gradual normalization of bile flow and hepatic function does follow.

More recently, glutamine has been proposed as a trophic factor for the bowel that may facilitate recovery after enterocolitis or extensive intestinal resection. Adding glutamine to TPN solutions may represent a beneficial therapeutic intervention to prevent or alleviate TPN-associated liver dysfunction. Other data from TPN-dependent adult patients, as well as experimental animals, suggest that gut flora contribute to hyperalimentation-related hepatotoxicity. Studies using metronidazole, polymyxin B, or oral gentamicin to alter intestinal bacterial flora have all demonstrated some improvement in parenteral nutrition-associated cholestasis.
Specifically, each of these agents reduces the production of certain hepatotoxic by-products, such as enterotoxin, lithocholate, and tumor necrosis factor, of the bacterial overgrowth that occurs in the absence of enteral feedings.

In summary, the hepatotoxicity associated with hyperalimentation in the newborn is an iatrogenic condition for which preterm infants, and especially those requiring more than two weeks of TPN, are at greatest risk. It can be detected early by routine monitoring of liver functions, and is best managed by optimization of overall nutrition and growth, and earliest-possible implementation of enteral feeds.

References


