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EDITORIAL

The Risk Factors of Parenteral Nutrition-associated Cholestasis in Preterm Infants

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Preterm infants are at a higher risk for developing nutritional compromise because of limited nutrient reserves, immature gastrointestinal function, and greater nutrient demands. The introduction of parenteral nutrition (PN) in early postnatal life has improved their mortality and morbidity and is now widely used in neonatal intensive care units (NICUs). However, prolonged PN is associated with a wide spectrum of hepatobiliary derangements, and cholestasis is a major complication in preterm infants. Parenteral nutrition-associated cholestasis (PNAC) is defined as cholestasis (conjugated bilirubin $\geq$2.0 mg/dL) that is associated with a prolonged duration of PN administration (usually $>$2 weeks).[1,2] Accurate diagnosis should be made only after other known causes of cholestasis have been excluded.

In this issue of *Pediatrics and Neonatology*, Hsieh et al retrospectively reviewed 62 preterm infants who received PN for at least 14 days and who were admitted to their NICU between 2004 and 2007.[3] Their reported incidence of PNAC was 17.74% (11 infants), which is comparable with another report in Taiwan.[4] The authors found that the most significant risk factor and predictor for the development of PNAC was the duration of PN. The cut-off point estimated by ROC curve was 61 days. Because the duration is too long to serve as a good predictor, the authors concluded that low energy intake during the 2nd and 3rd weeks of life can be a predictor of PNAC.

Although PNAC has been well documented for more than 30 years, the precise etiology is still not fully understood.[1,5] The pathogenesis is considered to be multifactorial, and includes hepatic immaturity, loss of enteral feeding, sepsis, and PN toxins and/or deficiencies.[6] The high prevalence of PNAC in younger age groups, particularly premature infants, suggests the pathogenic role of immature organ functions, such as the biliary secretory system, decreased bile acid pool, impaired hepatic mitochondrial function, and enterohepatic circulation.[5] The duration of PN is also related to the severity of histopathological changes in the liver. In an autopsy series, Zambrano et al found that, while the duration was $<$2 weeks, no fibrosis or only mild fibrosis was observed. However, in the patients who received PN for more than 6 weeks, moderate-to-severe hepatic fibrosis developed.[7] The risk associated with longer duration of PN exposure was also observed in clinical studies, as highlighted in this paper.[3]

In 1975, Rager and Finegold reported intrahepatic cholestasis in 9 out of 15 premature infants who received PN.[8] This observation was the first indication that lack of enteral intake may contribute to PNAC. Enteral starvation could subsequently lead to the lack of cholecystokinin release, decreased emptying of the gallbladder, followed by bile stasis and depletion of the enterohepatic circulation.[1,5,9] Hypoplasia of enterocytes and impaired gut immunity also contribute to PNAC via inflammatory pathways. In the current study, the risk of delayed enteral feeding was reflected by the low energy intake during the 2nd and 3rd weeks of life.[3] The investigators' results further support the protective effect of early enteral feeding.

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Sepsis has a crucial role in the development of PNAC. The requirement for central line placement for PN infusion, bacterial overgrowth caused by enteral starvation and immature immune function facilitate the occurrence of infection. The risk of sepsis, which has been observed both clinically and in animal models,[1,4,6,10] is also reported in this study. Although metronidazole and tetracycline therapy seemed to be beneficial in rodent models,[10,11] the clinical data in humans are limited.[12,13]

The components of PN also contribute to the pathogenesis of PNAC, including taurine and carnitine deficiency, aluminum and manganese toxicity, and oxidant imbalance.[5,6] The caloric excess caused by glucose and lipid overload may lead to elevated transaminase levels and hepatic steatosis. The protein content in PN is also associated with liver toxicity. One previous study reported that premature infants who received PN formulations with higher protein content (3.6 g/kg) developed cholestasis earlier than those who received 2.5 g/kg daily.[14] In addition, stigmasterol, a phytosterol that is prevalent in soy-derived PN lipid solutions, suppressed the expression of bile acid homeostatic proteins such as bile salt export pump, fibroblast growth factor-19, and organic solute transporter α/β.[15] There are several recent reports that have demonstrated that substituting a fish-oil-based lipid for the standard soy-bean preparation may be a useful strategy to treat PNAC.[16,17] Further randomized controlled studies are warranted to determine the efficacy and safety of this preparation.

Although effective therapeutic and preventive strategies for PNAC have not been established, some pilot studies have been reported with encouraging results. Ursodeoxycholic acid (UDCA, 10–30 mg/kg/day) appears to be effective in both a pilot study[18]and retrospective reports, [19,20] and is now widely used in NICUs. In one small prospective, double-blind, placebo-controlled trial, Arslanoglu et al reported that prophylactic use of UDCA in preterm infants who received PN could constantly and significantly reduce γ-glutamyl transferase activity over time.[21] This result suggests a preventive role of UDCA and warrants further investigation. High-dose oral erythromycin, used as prokinetic agent, appeared to provide some protection against the development of PNAC in a randomized trial in preterm infants.[22] The treatment was also associated with an earlier time to achieve full enteral feeding and reduce the number of cases with recurrent septicemia. However, the safety profile, including the influence of erythromycin on bowel microbiota and increased risk of pyloric stenosis, should be addressed before evaluating its prophylactic role. The favorable outcomes in these pilot studies call for further investigation of a preventive strategy for PNAC. Good predictors for the development of PNAC in preterm infants, as Hsieh et al tried to explore in the current study,[3] are important in clinical practice.

References

1. Drongowski RA, Coran AG. An analysis of factors contributing to the development of total parenteral nutrition-induced cholestasis. *JPEN J Parenter Enteral Nutr* 1989;13:586–9.
2. Kelly DA. Liver complications of pediatric parenteral nutrition: epidemiology. *Nutrition* 1998;14:153–7.
3. Hsieh MH, Pai W, Tseng HI, Yang SN, Lu CC, Chen HL. Parenteral nutrition-associated cholestasis in premature babies: risk factors and predictors. *Pediatr Neonatol* 2009;50:202–7.
4. Wu TJ, Teng RJ, Yau KI. Risk factors of cholestasis in very low-birth-weight infants. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1996;37:278–82.
5. Guglielmi FW, Regano N, Mazzuoli S, et al. Cholestasis induced by total parenteral nutrition. *Clin Liver Dis* 2008; 12:97–110, viii.
6. Carter BA, Shulman RJ. Mechanisms of disease: update on the molecular etiology and fundamentals of parenteral nutrition associated cholestasis. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:277–87.
7. Zambrano E, El-Hennawy M, Ehrenkranz RA, Zelterman D, Reyes-Mugica M. Total parenteral nutrition induced liver pathology: an autopsy series of 24 newborn cases. *Pediatr Dev Pathol* 2004;7:425–32.
8. Rager R, Finegold MJ. Cholestasis in immature newborn infants: is parenteral alimentation responsible? *J Pediatr* 1975;86:264–9.
9. Beath SV, Davies P, Papadopoulou A, et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. *J Pediatr Surg* 1996;31:604–6.
10. Lichtman SN, Keku J, Schwab JH, Sartor RB. Hepatic injury associated with small bowel bacterial overgrowth in rats is prevented by metronidazole and tetracycline. *Gastroenterology* 1991;100:513–9.
11. Freund HR, Muggia-Sullam M, LaFrance R, Enrione EB, Popp MB, Bjornson HS. A possible beneficial effect of metronidazole in reducing TPN-associated liver function derangements. *J Surg Res* 1985;38:356–63.
12. Kubota A, Okada A, Imura K, et al. The effect of metronidazole on TPN-associated liver dysfunction in neonates. *J Pediatr Surg* 1990;25:618–21.
13. Gunsar C, Melek M, Karaca I, et al. The biochemical and histopathological effects of ursodeoxycholic acid and metronidazole on total parenteral nutrition-associated hepatic dysfunction: an experimental study. *Hepatogastroenterology* 2002;49:497–500.
14. Vileisis RA, Inwood RJ, Hunt CE. Prospective controlled study of parenteral nutrition-associated cholestatic jaundice: effect of protein intake. *J Pediatr* 1980;96:893–7.
15. Carter BA, Taylor OA, Prendergast DR, et al. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. *Pediatr Res* 2007;62:301–6.
16. Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 2008;121: e678–86.
17. Cheung HM, Lam HS, Tam YH, Lee KH, Ng PC. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. *Clin Nutr* 2009;28:209–12.

18. Spagnuolo MI, Iorio R, Vegnente A, Guarino A. Ursodeoxycholic acid for treatment of cholestasis in children on long-term total parenteral nutrition: a pilot study. *Gastroenterology* 1996;111:716–9.
19. Levine A, Maayan A, Shamir R, Dinari G, Sulkes J, Sirotta L. Parenteral nutrition-associated cholestasis in preterm neonates: evaluation of ursodeoxycholic acid treatment. *J Pediatr Endocrinol Metab* 1999;12:549–53.
20. Chen CY, Tsao PN, Chen HL, Chou HC, Hsieh WS, Chang MH. Ursodeoxycholic acid (UDCA) therapy in very-low-birth-weight infants with parenteral nutrition-associated cholestasis. *J Pediatr* 2004;145:317–21.
21. Arslanoglu S, Moro GE, Tauschel HD, Boehm G. Ursodeoxycholic acid treatment in preterm infants: a pilot study for the prevention of cholestasis associated with total parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:228–31.
22. Ng PC, Lee CH, Wong SP, et al. High-dose oral erythromycin decreased the incidence of parenteral nutrition-associated cholestasis in preterm infants. *Gastroenterology* 2007;132: 1726–39.