Liver Disease in Patients on Total Parenteral Nutrition

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KEYWORDS

• TPN • PNALD • Cholestasis of sepsis • Combined intestinal and liver failure

KEY POINTS

- Parenteral nutrition-associated liver disease (PNALD) is defined as a spectrum of liver disease ranging from abnormal liver enzymes to steatosis, to fibrosis, and eventual cirrhosis in patients on total parenteral nutrition (TPN).
- The causes of PNALD are multifactorial.
- Diagnosis of PNALD in adults is primarily by exclusion, given concomitant risk factors of critical illness and postoperative state that are present in hospitalized patients on TPN, such as sepsis, hypoxia, multiple medications, and biliary causes.
- Treatment of PNALD involves avoiding TPN if possible, or otherwise incorporating fish oil–based lipid emulsion in the TPN formulation, based on recent promising research on the latter's role in reducing risk and progression of liver disease.
- In patients with intestinal and liver failure, a combined intestine-liver transplant remains a viable option.

INTRODUCTION

Total parenteral nutrition (TPN) is defined as parenteral (intravenous [IV]) nutritional support that includes calories, amino acids, electrolytes, vitamins, minerals, and trace elements. TPN is indicated in patients for a variety of conditions revolving around intestinal insufficiency due to decreased intestine length or functionality. Most commonly, it is used in patients with short gut syndrome. Congenital causes are observed in infants born with intestinal atresia, whereas acquired causes are likely related to surgery involving small intestine resection. The latter may be in the setting of Crohn's disease or small bowel ischemia related to thrombosis, volvulus, or trauma. Functional short bowel syndrome can occur in chronic intestinal pseudo-obstruction syndrome, refractory celiac sprue disease, radiation enteritis, or congenital villous atrophy. TPN is also indicated for those with malnutrition during critical illness, and

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bowel obstruction. Studies have shown that the length of remnant intestine necessary to prevent TPN dependence is approximately 100 cm in the absence of an intact and functional colon, or approximately 50 cm in the presence of a completely functional colon.[1–2]

TPN is generally administered via central venous access, such as a peripherally inserted central catheter, port, or Hickman catheter. The need for central access stems from the toxicity of TPN to smaller peripheral veins due to the pH, osmolarity, and volume of the nutritional solution. There are several side effects and adverse effects associated with the administration of TPN. These include thrombosis of central veins and catheter-related bloodstream infections, such as fungemia, cholecystitis, and metabolic disease. This article discusses the impact of TPN on the liver and its function.

Parenteral nutrition-associated liver disease (PNALD) is a spectrum of disease that can range from mild liver enzyme abnormalities to steatosis to eventual fibrosis or cirrhosis. In general, PNALD is more prevalent in infants than in adults. In infants, especially those with low birthweight, up to 50% to 66% of those on TPN have been reported to develop PNALD.[3–6] An even higher incidence is observed in premature infants, postulated to occur because of insufficient capacity for hepatic transsulfuration, the latter being important in the metabolism of nutritional byproducts.[7–9] One study showed 65% of infants on TPN developed cholestasis and 13% eventually progressed to hepatic failure.[10] The prevalence and incidence of PNALD have not been as clearly delineated in adults as in the pediatric population. PNALD remains primarily a diagnosis of exclusion in adults on TPN.

PATHOPHYSIOLOGY

The pathophysiology of PNALD has been studied in great detail, and seems to be multifactorial in causes. The fatty acid derivatives of lipid emulsions have been shown to have an impact on systemic inflammation and oxidative stress, which can lead to liver damage.[11] It is also postulated that prolonged bowel rest with subsequent bacterial overgrowth may contribute to hepatic steatosis and cholestasis.[12,13] In patients with severe protein malnutrition, hepatic steatosis can develop because of decreased very low-density lipoprotein (VLDL) production, which results in hepatic triglyceride accumulation.[14–16]

Deficiency in choline can also result in hepatic steatosis. The proposed mechanism of this is impaired biosynthesis of choline from methionine when the latter is provided parenterally. Reversal of liver injury was seen to occur with choline supplementation within TPN solution.[14,15] Taurine deficiency is another postulated cause of PNALD, with serum levels being decreased due to cystathionase deficiency with TPN.[17–19]

Another postulated cause for the development of PNALD is toxicity from other nutrients infused in TPN. Particularly, infusion of greater than 50 kcal/kg/d of dextrose can lead to hepatic steatosis through an increase in the portal insulin or glucagon ratio.[20] Increased insulin leads to increased lipolysis and decreased hepatocyte excretion of triglycerides, in addition to inhibition of mitochondrial fatty acid oxidation, which then contributes to accumulation of fatty acids in hepatocytes.[20,21] The latter was demonstrated in a study in which glucagon was added to TPN formulation, with subsequent decrease of the insulin or glucagon ratio that prevented the development of steatosis in rats.[22,23] The lipid component in the formulation is also thought to play a role. One study determined that dosage of IV soybean oil–based lipid emulsion (SOBLE) correlates with cholestasis in children on long-term TPN, with some evidence that lipid dose greater than 1 g/kg was associated with PNALD in adults. IV fat