BAPEN
Putting patients at the centre of good nutritional care

Top Tips for Managing Abnormal Liver Function Tests in Patients Receiving Parenteral Nutrition

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Derangement of liver function tests (LFTs) is common amongst patients receiving parenteral nutrition (PN) and is currently more common in the paediatric population. There is a broad spectrum of disease ranging from transient elevation in the liver enzymes in those receiving short-term PN, through to cirrhosis and liver failure in those who require long-term PN. The aetiology of liver disease is multifactorial, relating to both the patient and nutritional factors, and hence the term intestinal failure-associated liver disease (IFALD).

Key points

1. Identify other causes of abnormal LFTs; PN is not the most common cause. Sepsis, drug therapy and pre-existing liver disease, are common aetiologies
2. Paediatric patients often present with cholestatic LFTs
3. An excess of any of the macronutrient components of PN can cause abnormal LFTs
4. Continuous PN is more associated with abnormal LFTs than cyclical PN
5. First-generation, soya bean-based lipid preparations are associated with most LFT abnormalities
6. An excess of copper, manganese, or aluminium can cause abnormal LFTs
7. Deficiencies of choline, taurine, carnitine or essential fatty acids can cause abnormal LFTs
8. Treatment addresses the factors above and consideration is given to maximising oral/enteral feeding, cyclical PN, changing bile composition (URSO) and occasionally antibiotic therapy
9. Severe IFALD-associated liver failure is an indication for small bowel transplantation.

Explanations

A. There are many other contributors to abnormal LFT in patients with intestinal failure who require PN. Pre-existing liver disease can be identified in up to a third of such patients prior to initiation of PN. Drug-related causes of elevated LFTs should be identified (e.g. antibiotics, antifungals and proton pump inhibitors). Sepsis commonly causes abnormal LFTs in adults on PN and in neonates causes cholestasis. Small bowel bacterial overgrowth can lead to cholestasis and portal endotoxaemia. Specific to the intestinal failure population, the residual small bowel length in continuity is important. Small bowel length <100 cm may be associated with abnormal LFTs, while length <50 cm may be associated with cholestasis. Periods of biliary stasis (due to surgery, nil by mouth or drugs) predispose to biliary sludge and thus to gallstones.

B. Paediatric patients with intestinal failure used to have a higher prevalence of severe IFALD; and a quarter of those advanced to end-stage liver failure. Intrahepatic cholestasis and hyperbilirubinaemia are the hallmark of IFALD in this population, which is uncommon in the adult population.

C. An excess of energy in the form of glucose, protein and/or lipid can result in abnormal LFTs. Excessive glucose infusion causes hyperinsulinaemia, which inhibits fatty acid oxidation, and so may result in hepatic steatosis. Replacement of a proportion of the glucose energy with lipid reduces steatosis, but excessive parenteral lipid may also cause abnormal LFTs. Proposed mechanisms include a limited ability of administered lipid to undergo lipolysis due to a reduced cholesterol content, an accumulation of phytosterols, and an increased production of pro-inflammatory mediators due to a high linoleic acid content. Excessive amino acids may promote cholestasis in neonates.

D. First-generation soya bean-based lipid emulsions have been available for clinical use for over 60 years. Thus, the complications of excess lipid administration described above have been well documented in those receiving such preparations, even at modest levels. Comparatively, second-generation (medium-long chain triglycerides and monounsaturated fatty acids) and third-generation (fish oil-based; mixed lipid emulsions) preparations may be associated with less hepatotoxicity. Available comparative literature suggests an improvement in cholestasis and a reduction in morbidity and mortality, although further definitive studies are required. There has been much interest in the role of phytosterols (plant-derived sterols similar to cholesterol) in the aetiology.

E. Copper and manganese are important trace elements in multiple physiologic processes, but accumulation within the liver is hepatotoxic. Both substances are excreted via the biliary route and may accumulate in the setting of pre-existing cholestasis. Aluminium serves no known physiologic function in humans and the gut absorbs <1% of the amount ingested. When present in PN solutions, however, this mechanism is bypassed, which can allow accumulation and hepatotoxicity (as well as neurotoxicity, anaemia, and bone disease). The aluminium content of PN preparations results from its presence in calcium gluconate and inorganic phosphate additives.

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F. Choline is required for very low-density lipoprotein synthesis within the liver, and hence the export of hepatocyte triacylglycerol. Deficiency of choline therefore results in hepatic steatosis and has been associated with elevated aminotransferase levels in those receiving PN. Small placebo-controlled studies of parenteral choline supplementation have shown reversal of these abnormalities (choline is not available in the UK). Taurine is an important component of bile salt conjugation pathways, and deficiency has been associated with cholestatic liver disease, particularly in neonates and pre-term infants. Parenteral supplementation of taurine prevents neonatal liver disease, but to date has shown no benefit in adult IFALD. Carnitine aids in the mitochondrial transport of long-chain fatty acids, and severe deficiency can result in hepatic steatosis.

G. Cyclic PN (usually PN given during night time only) is associated with less LFT abnormalities than continuous PN.

H. Given the causes of liver dysfunction outlined above, treatment is aimed at ameliorating identified causative factors. Sepsis must be treated expediently, and efforts made to reduce its occurrence, particularly in relation to central venous catheter infections. Culprit medications should be identified and stopped if possible. Review and optimisation of the composition of PN solutions should be performed at regular intervals to adjust for individual patient requirements. Maximising oral and/or enteral nutrition will improve gut function and gut hormone release, and reduce bacterial overgrowth and biliary stasis. Changing the lipid preparation to second or third-generation formulations can be considered. Cyclical, rather than continuous, PN infusion should be the rule to minimise the effects of prolonged hyperinsulinaemia. Altering bile composition with ursodeoxycholic acid has shown benefit in neonatal IFALD, but there is no evidence of long-term benefit in adult disease. Antibiotics to treat bacterial overgrowth may reverse some LFT derangement.

I. Referral for small bowel transplantation should be considered in impending or overt liver failure due to IFALD. It is one of the commonest reasons for performing intestinal transplantation. In end-stage liver disease, combined liver and small intestinal transplantation can be performed. In neonatal IFALD, intestinal adaptation may allow for complete weaning of PN with time, and therefore single-organ liver transplantation may be considered.

Suggested reading

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