Liver Biopsy in HPN Patients – When, how and why?

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Intestinal failure associated liver disease (IFALD) is a major consequence of long-term parenteral nutrition (PN) and chronic intestinal failure (IF). In paediatric patients and young adults it may manifest as predominantly cholestasis, while in adults it is often characterised by steatosis/steatohepatitis or a mixed picture of cholestasis and steatosis. In both, progressive fibrosis leading to cirrhosis can also occur. One of the goals of intensive intestinal rehabilitation is to prevent progression of IFALD, so all members of the multiprofessional intestinal rehabilitation teams (MPIRT) should be aware of the diagnosis and management of this condition.

A key consideration in managing IFALD is knowing when to refer a patient for intestinal transplant. Historically, this was only considered when a patient developed overt liver failure and required a combined liver/intestinal graft, often with poor outcomes. It has become apparent that transplanting an intestine only and weaning the patient from PN, at earlier stages of fibrosis, results in improvement in the liver disease. Isolated intestinal transplants are technically easier, associated with shorter lengths of stay, less complications and greatly improved survival compared to combined grafts.

No non-invasive test has been validated for use in IFALD. Hence, liver biopsy for histological diagnosis and staging are required. Appropriate consideration should be given before asking a patient to have a biopsy, but overall these are safe and well tolerated with a very low complication rate in expert hands.

Key points

1. An intra-operative liver biopsy is not routinely recommended for patients undergoing an extensive enterectomy nor is a routine cholecystectomy. A liver biopsy should ideally be discussed as part of the MPIRT planning of IF surgery.
2. No non-invasive method for diagnosing liver fibrosis has been demonstrated to be useful in diagnosing or staging IFALD.
3. Consider liver biopsy in all home parenteral nutrition (HPN) patients with ultrashort bowel (<20 cm residual small bowel) who have been on PN for a year or longer and may be a candidate for intestinal transplant.
4. Repeat, after MPIRT discussions, liver biopsy every 2-3 years in patients with ultrashort bowel who have not already been referred to an intestinal transplant centre.
5. Consider liver biopsy in all HPN patients with a second liver insult (including but not limited to, known or suspected previous NAFLD, viral hepatitis, or excessive alcohol intake) who have been on PN for 2 years or more.
6. For any patient with moderate or severe fibrosis, refer urgently to an intestinal transplant centre.
7. For any patient with mild fibrosis, consider repeat liver biopsy in 2-5 years, depending on overall risk. The decision on surveillance intervals can be made in conjunction with a transplant centre.

Explanations

1. Although it may be helpful, we do not recommend a routine baseline intra-operative liver biopsy (to stratify future risk) because of the added risks of bleeding from the biopsy and the biopsy itself likely to show non-specific changes associated with acute illness/sepsis/shock. Patients with intestinal failure are at higher risk of developing gallstones (often pigment type), with 45% of short bowel patients (especially men) having or having had them. Awareness of this amongst surgeons means some patients undergoing extensive enterectomy have a cholecystectomy at the index operation. We do not recommend this. However, cholecystectomy may be considered alone or as part of an elective operation if gallstones are present. For IF patients undergoing cholecystectomy or other abdominal surgery, an intra-operative liver biopsy should be considered if technically possible (unless the surgery is undertaken with the expectation of weaning the patient from PN).

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2. Non-invasive tests for diagnosing liver fibrosis have gained popularity in other aetiologies of liver disease, but none have been validated in IFALD. Transient elastography (Fibroscan®) in particular seems an attractive method, but two studies have shown it is not reliable. As the elastography component on Fibroscan® relies on liver stiffness, which will be influenced by portal inflow, it is perhaps not surprising that it is unreliable in patients with intestinal failure, who do not have normal mesenteric/portal haemodynamics.

   Certain biochemical panels have been proposed as non-invasive methods to detect fibrosis, including FIB-4, ELF, APRI. The FIB-4 (Fibrosis-4) index and APRI have been shown to correlate with known IFALD risk factors in very small studies, but no correlation with histology was made. The only other method to show correlation with IFALD risk factors is the LiMAX test, a dynamic test that measures metabolism of 13C labelled methacetin, but this measures liver functional capacity rather than the degree of fibrosis. However, it is useful in predicting outcome after liver resection and may be worth further evaluation.

3. Ultrashort bowel is defined as a residual small bowel length of 20 cm or less, from the duodeno-jejunal flexure to an end jejunostomy. These patients are at particularly high risk for the development of IFALD. The reasons for this are not completely understood, but these patients are more likely to have high glucose and lipid content in their PN due to (almost) complete lack of enteral nutrition. They also have minimal portal venous inflow to the liver, significant alterations/reductions in the microbiome and complete disruption of the enterohepatic circulation of bile salts, which may all influence the development of liver disease.

4. Progression of fibrosis in ultrashort bowel can occur very quickly. Sequential biopsies can facilitate referral of the patient for intestinal transplant at the optimum time. From a purely histological perspective the best time to refer is when there is moderate fibrosis (Ishak 3/4), though there are other medical, surgical and psychological factors that must be considered in each individual patient. Early discussion with a transplant centre is always recommended.

5. A small proportion of HPN patients will have co-existing liver disease or significant risk factors for other liver pathologies. This may include chronic viral hepatitis, biliary disease (particularly those with underlying inflammatory bowel disease) or autoimmune/metabolic liver disease. An under-recognised group is probably those patients with IF following complications of bariatric surgery, who may have a combination of IFALD and NAFLD. For these patients with a ‘second hit’ to the liver, there should be a lower threshold for liver biopsy.

6. It has become apparent that for patients with pre-cirrhotic IFALD-related fibrosis, an isolated intestinal transplant can halt progression or even reverse the degree of fibrosis. These transplants are technically easier, associated with shorter lengths of stay, fewer complications and greatly improved survival compared to combined liver/intestine grafts. If we can diagnose IFALD at these earlier stages, we can also ‘save’ a liver graft for those waiting on the liver transplant list.

7. If a patient is at risk of IFALD, but initial biopsy shows very early disease then a balance needs to be struck between too early a referral for transplant and ‘missing the boat’. These decisions are perhaps best made jointly, by the IF team and the transplant centre.

Suggested reading:

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