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Review Article

Pediatric liver transplantation

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ABSTRACT

Liver transplantation is now an effective therapy for children with end stage liver disease. The commonest indications include cholestatic (biliary atresia, progressive familial intrahepatic cholestasis) and metabolic diseases. In selected patients it is also life saving treatment for fulminant hepatic failure. Innovations like the split retrieval technique yields two grafts from a single donor and expands the donor pool. The most common complications in the immediate post-operative period are bleeding, portal vein thrombosis and hepatic artery thrombosis. Effective immunosuppression improves survival but its long-term use is associated with complications. The patient and graft survival rates are excellent and have been improving continuously over the last two decades.

1. Introduction

Liver transplantation is an effective & widely accepted therapy for children with end stage liver disease and it has brought about a dramatic change to the prognosis of many of them with metabolic diseases and liver failure. Initially, in the early 1980s, it was an experimental procedure performed in a few centers in the world but by the mid 1990s there were more than 100 centers in the United States of America alone performing more than 3000 liver transplantations every year. As the procedure evolved with surgeons becoming more skilled and more effective immunosuppressive drugs available patient survival has improved to 90% at 1 year and 75% at 15–20 years with a relatively good quality of life.[1]

Liver transplantation is now enabling many children who previously had otherwise fatal diseases to survive with most of them growing into adulthood. However, as with any other medical or surgical innovations, transplantation also carries with its own problems which need to be considered and this mainly concerns the necessity for long-term immunosuppression and its attendant side effects. This is why the thrust of much research on this subject is to look at the possibility of complete weaning a pediatric liver recipient off immunosuppression and achieve graft tolerance. There are also groups who are looking into other issues including psychological and social adjustments that have to made by the recipients while progressing to adulthood.

2. Indications

Liver transplantation is used as the end therapy for many metabolic and congenital diseases of the children which

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would otherwise be fatal. Its indications may be broadly divided into six groups. These include

1. Cholestatic diseases
   a. Biliary atresia
   b. Progressive Familial Intrahepatic Cholestasis (PFIC)
      i. PFIC-1
      ii. PFIC-2
      iii. PFIC-3 (Multidrug resistance associated protein 3 (MDR3) deficiency)
   c. Alagille's syndrome
   d. Non-syndromic bile duct paucity
   e. Total parenteral nutrition associated liver disease
2. Metabolic diseases
   a. Wilson's disease
   b. Alpha 1-antitrypsin deficiency
   c. Tyrosinemia
   d. Hemochromatosis
   e. Crigler–Najjar syndrome
   f. Glycogenosis
   g. Hyperoxaluria
   h. Metabolic respiratory chain deficiencies
   i. Familial hypercholesterolemia
   j. Methylmalonyl aciduria
3. Chronic hepatitis
   a. Autoimmune hepatitis
   b. Sclerosing cholangitis
   c. Viral hepatitis
4. Other liver diseases
   a. Fibropolycystic liver disease
   b. Budd–Chiari syndrome
   c. Cryptogenic cirrhosis
5. Acute liver failure
6. Liver tumors

Biliary cirrhosis due to biliary atresia is the most common indication for transplantation. Portoenterostomy (the Kasai Procedure) is usually performed within 90 days after birth. Infants older than 90 days may also benefit from the Kasai operation, but a careful histological examination should be done to rule out significant liver damage. The Kasai procedure has usually been performed in the majority of patients before they come for transplantation but biliary atresia may progress towards end stage liver disease. So patients in whom the Kasai operation has failed or who have had no previous surgical intervention have a clear indication for transplantation. Among others in whom it has been initially successful, upto 50% of patients have to be transplanted by the age of 10 because they have progressed to chronic liver failure.[2]

For *intrahepatic cholestatic diseases* (Alagille's syndrome, progressive familial intrahepatic cholestasis, and sclerosing cholangitis) or sclerosing cholangitis, liver transplantation is indicated to eliminate severely debilitating symptoms, such as pruritus.

Progressive Familial Intrahepatic Cholestasis is an autosomal recessive inherited syndrome caused by the absence of a gene product required for canalicular export and bile formation. It is recognized during infancy and usually progresses to cirrhosis within the first decade of life. The average age at onset is 3 months – although some patients do not develop jaundice until adolescence. PFIC can progress rapidly and cause cirrhosis during infancy or may progress slowly with minimal scarring. Specific gene defects have been identified for three subtypes of PFIC. PFIC1 (previously called as Byler's disease) and PFIC2 are characterized by low gamma-glutamyl peptidase (GGT) levels. Though genetically distinct, PFIC1 and PFIC2 are clinically similar. In PFIC3, patients have deficient hepatocellular phospholipid export. Its clinical presentation is the same as PFIC1 and 2 but PFIC3 is associated with an elevated serum GGT. In patients with PFIC, therapeutic options are limited although biliary diversion sometimes leads to relief of the severe pruritus. If this operation fails, liver transplantation remains the only option.

Alagille's syndrome is an autosomal dominant genetic disorder that affects the liver, heart, kidney, and other systems of the body. Problems generally become evident in infancy or early childhood. In more than 90 percent of cases mutations in the *JAG1* gene cause Alagille syndrome. Some individuals have small deletions of genetic material on chromosome 20 that include the *JAG1* gene and mutations in a different gene *NOTCH2*. Indications for consideration of liver transplantation include progressive hepatic dysfunction, severe portal hypertension, failure to thrive, intractable pruritus and osteodystrophy.

Other indications for liver transplantation in children are *chronic active hepatitis with cirrhosis*, *cirrhosis caused by liver injury in certain metabolic diseases* and *fulminant hepatic failure* which is more commonly drug induced in children. Cirrhosis itself is not an immediate indication unless the patient has features of liver decompensation i.e. coagulopathy unresponsive to Vitamin K therapy, refractory ascites, hepatorenal syndrome, gastrointestinal bleeding, growth failure and frequent and severe bacterial infections.

The natural history of the disease is the key factor which determines the development of decompensated disease and the need for transplantation.

Inborn errors of metabolism are the second most common indication for hepatic transplantation; α1-antitrypsin deficiency being the most common in this group. Other metabolic disorders for which transplantation is indicated are tyrosinemia, Wilson's disease, glycogen storage disease, and familial hypercholesterolemia.

Less frequent indications are *congenital hepatic fibrosis, postnecrotic cirrhosis, secondary biliary cirrhosis, neonatal hepatitis, and malignancy*.

Liver transplantation is also the most effective therapy for *fulminant hepatic failure*. However it is difficult to determine whether a patient in failure might recover without transplantation so the decision for transplantation is based on the cause of the liver failure and other factors with which it is associated. To ease these decision protocols, scores and criteria have been developed which help in predicting which patients will need a transplant i.e. those in whom the outcome will be fatal without one. The predictive factors for a poor