

LIVER TRANSPLANTATION IN CHILDREN

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Abstract: Liver transplantation is now an established mode of therapy in children with fulminant hepatic failure and end stage liver disease due to various causes. The indications have evolved over the last few years to include various metabolic disorders. A thorough pre transplant evaluation followed by pre-emptive identification and management of anticipated complications is essential for the success of a liver transplant. Low socio economic and education levels and insufficient social assistance have a considerable impact on the practicality of a transplant taking place in India. The liver transplant programme in India has come a long way over the past 10 years with patient survival rates comparable to the best centers in the world. The improvements in surgical and medical expertise have contributed in a big way to this achievement.

INTRODUCTION

Paediatric liver transplantation (LT) is now an established therapeutic procedure for children with fulminant hepatic failure and end stage liver disease due to diverse etiologies. The survival has improved significantly over the last decade with pediatric recipients faring better than adults¹. Initially this therapeutic modality was available only in developed world but over the past decade pediatric liver transplantation has become established in India with survival rates comparable to that of established centers in the West^{2,3}. The medical and surgical expertise gained over the past few years has allowed the application of liver transplantation to even very young infants with excellent results.

THE NEED FOR PEDIATRIC LIVER TRANSPLANTATION

In the West approximately 2-3 pediatric liver transplants are performed per million of population per year. At this rate, around two to three thousand children need liver transplantation in India annually. Out of 2436 hepatobiliary referrals to our centre in last 10 years, 256 children satisfied the criteria for liver transplant. As in the West, extrahepatic biliary atresia (EHBA) was the commonest indication with over 60 percent of children requiring LT (Table 1). In India however, most children with EHBA are either diagnosed late or have not undergone the Kasai procedure at all. At another tertiary care center, nearly 70 percent babies with EHBA required LT based on internationally accepted criteria². Internationally, the donor pool for children has been extended by the use of cadaveric cut-down, split and living-related transplantation to match the increasing pool of potential liver transplant recipients³. In India, however, majority of liver transplants are living related liver transplants^{4,5}.

INDICATIONS FOR LIVER TRANSPLANTATION

The indications for a transplant have increased over the last few years to include various metabolic disorders (Table 2). While biliary atresia continues to be the commonest indication for a pediatric liver transplant world over, more and more children with diverse etiologies are being offered this life saving modality with successful results.

Chronic liver failure

Chronic liver failure secondary to cholestatic liver disease is the most common indication for liver transplant in children. The single most common cause for chronic liver failure in infancy and childhood is **biliary atresia**. The Kasai procedure is successful in one-half of all patients and

Table 1: Liver transplant indications at Indraprastha Apollo Hospital, New Delhi (1/10/1997 to 24/10/08)

Total Hepatobiliary referrals 2436	
Criteria for transplant satisfied 256 (12.5%)	
Neonatal cholestasis syndrome	156
Fulminant hepatic failure	44
Cryptogenic	27
Wilson's disease	07
Hepatoblastoma	05
PFIC	06
Tyrosinemia	04
Hepatocellular carcinoma	03
Budd Chiari syndrome	02
Crigler Najjar syndrome	01

Table 2 Indications for Liver transplantation in children; Chronic liver failure

A) Cholestatic liver disease

Biliary atresia
Idiopathic neonatal hepatitis
Progressive familial intrahepatic cholestasis
Bile duct hypoplasia

B) Metabolic liver disease

Wilson disease
Tyrosinemia type I
Glycogen storage disorder type IV
Cystic fibrosis

C) Chronic hepatitis

Autoimmune
Idiopathic
Cryptogenic cirrhosis
Post viral (Hepatitis B, C)
Fibropolycystic liver disease ± Caroli's disease

Acute Liver failure

A) Fulminant hepatic failure

Viral hepatitis
Acetaminophen poisoning

B) Metabolic liver disease

Fatty acid oxidation defects
Neonatal hemochromatosis
Tyrosinemia type I
Wilson disease

Inborn error of metabolism

Crigler-Najjar syndrome type I
Organic acidemias
Primary hyperoxaluria
Urea cycle defects
Hepatic Tumors
Benign tumors

Unresectable malignant tumors with no extra-hepatic spread

if jaundice is fully relieved, most children will grow and develop normally but by age of 10 years about 50% of these patients need a transplant for chronic liver failure⁶. While 21 % of all hepatobiliary referrals at our centre were of neonatal cholestasis, nearly 20% of these had biliary atresia. Of all the children who received the transplant, 29 % had a diagnosis of biliary atresia. The outcome of cholestatic liver diseases like Progressive Familial Intrahepatic Cholestasis (PFIC) is more variable. Liver transplant is indicated if **decompensated cirrhosis** and/or **intractable portal hypertension** develop, if malnutrition and growth failure are unresponsive to nutritional support or if there is intractable pruritis that is resistant to maximum medical therapy or biliary diversion. Ten percent of children who underwent LT at our centre had diagnosis of PFIC.

Metabolic disorders

Wilson disease is a rare indication of liver transplant in childhood. Early diagnosis and therapy with penicillamine should be curative, but many children present with established cirrhosis. Liver transplant is indicated in children who present with advanced liver disease, progressive hepatic disease despite medical therapy or fulminant hepatic failure. The clinical presentation of Tyrosinemia type-I includes both acute and chronic liver disease and multiorgan failure. It constitutes an important metabolic indication for liver transplant both in the infantile and older age groups. Metabolic disorders constituted less than 5% of children requiring LT at our centre in last 10 years. Early identification of these disorders is essential before severe extra hepatic manifestations ensue. A number of inborn errors of metabolism are secondary to hepatic enzyme deficiencies that lead to severe extra hepatic disease while the liver function remains normal. Crigler Najjar syndrome type-I, primary hyperoxaluria are some of the examples of such disorders. A liver transplant is required in these cases to prevent or reverse extra hepatic disease. The timing of transplant in these cases depends on the rate of progression of the disease, the quality of life of the affected child and the development of severe irreversible extra hepatic disease.

Acute liver failure

Acute liver failure (ALF) is a rare condition in children, although it is associated with significant mortality without transplantation. Kelly et al found that 50% of acute liver failure in pediatric patients was due to an infection with more than half of these diseases being non-A-non-B-non-C-hepatitis⁷. In India, Hepatitis A is the commonest cause of ALF in children⁸. Metabolic diseases like Tyrosinemia type-I and Wilson disease can also present as acute liver failure, especially in the first year of life. The criteria from King's College London are widely used to assess for LT and comprise of 4 variables: leukocyte count >9000/ cu mm, bilirubin 13.8 mg/dl, age below 2 years and INR 4. If one of these variables appears in a child with acute liver failure mortality rises dramatically to 76%. In the case of the appearance of 2 variables mortality rises to 93% and with the presence of 4 variables mortality is 100%. ALF is the second most common indication among the children who required the transplant at our centre. While ALF was the presentation in 4 % of children referred to our centre during the last ten years, nearly 50 % of these satisfied the Kings College criteria for a transplant.

PRE-TRANSPLANT ASSESSMENT

The aims of assessment for liver transplantation are to confirm the diagnosis and severity of disease, define the patient's general medical status, arrange interim supportive care and assess socioeconomic and educational status of the family. Assessment is carried out by a multi-disciplinary team and involves the patient and their families. The ability of the child's family to comply with instructions and follow-up plans are relevant factors which must be considered in the transplant assessment process. Hepatic function is assessed by measurement of albumin and prothrombin time (synthetic function) and bilirubin, transaminases, alkaline phosphatase and gamma

glutamyl transpeptidase. The vascular anatomy is delineated by Doppler ultrasonography and/or MR or conventional angiography. A nutritional, developmental, cardiac and dental assessment is performed in all children. Serological examination is performed to assess immunity to viral pathogens.

PREPARATION FOR LIVER TRANSPLANTATION

The important aspects of the preparation are nutritional rehabilitation, immunization, treatment of hepatic complications and counseling.

Nutritional rehabilitation: Recent data suggests that preoperative nutritional status is an important factor affecting outcome post transplant¹⁰. Modular feeds which allow protein, carbohydrate and fat content to be individually prescribed for each child are recommended.

Immunization: It is essential to make sure that routine immunizations are complete. If necessary, immunization for MMR and varicella should be brought forward. However, in children undergoing emergency liver transplants, completing the immunization with live vaccines is not possible¹¹.

Treatment of hepatic complications: Ascites and fluid retention is managed by restricted sodium and fluid intake and the use of diuretic therapy. Bleeding varices are treated with intravenous somatostatin or octreotide, endoscopic band ligation or transjugular intrahepatic portal shunts. It is preferable to employ band ligation instead of sclerotherapy because of the potential risk of portal vein thrombosis and ulceration. Hepatic encephalopathy is treated by low protein diet and oral lactulose. The role of branched chain amino acids remains controversial and use of extracorporeal liver assist devices as a bridge to transplantation is not yet fully established¹².

Counseling: Education and counseling of the family and the child is of paramount importance to sustain them through the stressful procedure, the prolonged post-operative period and the life-long immunosuppressive therapy with its attendant risks and side effects

ICU CARE

In the immediate post operative period the main issues revolve around monitoring graft function (PT/INR, PTT and other liver function tests) in addition to maintenance of hemodynamic parameters, fluid balance and oxygenation to ensure adequate blood flow to the liver graft. Strict aseptic precautions must be followed in caring for transplant patients. Duration of mechanical ventilation in transplant recipient depends upon age and preoperative condition of the patient. A child with FHF may require a longer duration of ventilation depending on the neurological state. On the other hand, patients with normal pulmonary function preoperatively may require short term or no ventilation. Infants and small children are more likely to need postoperative ventilation. Ventilatory management aims at avoiding the respiratory complications of atelectasis, effusions and pneumonia. Some smaller patients may require a higher end expiratory pressure to compensate for a distended abdomen pushing onto the diaphragm. In a single centre series the mean time to extubation was 11.1 ± 15 hours and the mean duration of ICU stay was 7.2 ± 5.5 days¹³. Pain control is commonly achieved by opioid infusions titrated to effect. Judicious use of muscle relaxants might be needed. Atracurium (a non-depolarizing muscle relaxant metabolized by non enzymatic hydrolysis (Hoffman elimination) can be safely used. General principles of respiratory care apply in all mechanically ventilated patients. Close monitoring, early detection and treatment of complications remains the key to success in addition to supportive management by the liver transplant team.

COMPLICATIONS

Primary non-function is rare among living related liver transplant recipients.

It must however be closely monitored for the first 24 hours (rising transaminases, profound hypoglycemia and acidosis, coagulopathy, oliguria) requiring emergency retransplantation. Acute rejection occurs in first few weeks after transplantation (average 23 days after transplant in children) characterized by fever, increased bilirubin and liver enzyme levels and encephalopathy. Five to twenty percent patients will have vascular occlusion with accompanying graft loss. Vena cava, portal vein and more commonly hepatic artery may get occluded by intramural thrombus, or less commonly by extrinsic compression or vessel kinking. Vessels smaller than 3 mm diameter tend to have higher incidence of arterial thrombosis. Signs and symptoms consist of FHF, increased transaminase and bilirubin levels with worsening coagulopathy. Portal thrombosis presents with fulminant necrosis and intestinal edema with ascitis. Doppler ultrasonography and CT angiography are useful tools in early identification of vascular occlusion¹⁴. Early identification and management of bile leak and postoperative bleeding requires close monitoring.

IMMUNOSUPPRESSION

The usual immunosuppressive regimen consists of calcineurin inhibitors cyclosporine or tacrolimus and prednisolone along with mycophenolate mofetil (MMF). Tacrolimus based immunosuppression is preferred as it has been associated with less acute rejection and better long-term graft survival rates¹⁴.

INDIAN SCENARIO

Till a few years back, in the absence of LT facilities in India, a patient with liver failure had only two options, certain death or travel abroad for a transplant. Receiving a liver transplant in the West was not only a costly exercise but also entailed a long waiting period as being a foreigner, he/she would get a low priority on the cadaver waiting lists which were understandably biased to favor the state health entitled native population. The development of liver transplant programme in India led to an overall improvement in level of care in allied specialties (anesthesia, critical care, blood bank, radiology, histopathology) on one hand and on the other helped save precious foreign exchange^{15,16}. Our experience over the last 10 years has shown that it is possible to establish a programme but there are certain unique hurdles that need to be overcome^{15,16}. The social evaluation in our setting is extremely important. Low socioeconomic and educational levels along with insufficient social assistance have a considerable impact on practicality of a transplant taking place in India. Most patients are referred late for a transplant, quite often when they are not transplantable (Table 3). The sub optimal management of the patients in the pre transplant phase results in a sizeable number being unfit for transplantation^{15,17,18}. Cost is still a formidable problem for most patients and absence of medical insurance and state funding further aggravates the problem. A pediatric LT at our center costs between 12 to 15 lakhs, which is roughly one-tenth of what it would cost in the West. Despite these huge difference in costs, contributions from philanthropic organizations and medical insurance are required if LT is to become available to the vast majority of patients in India. There is a clear bias against the girl child with most families hesitating to spend on transplantation for a girl (Table 4). There is a paucity of reliable cadaver organ supply primarily due to low awareness about organ donation. With an appropriate brain death law already in place, sufficient public and professional education is needed to develop cadaver donation. More awareness and acceptability towards organ donation in our country is required so that cadaver organs are available for patients in urgent need for a transplant. Till then, living related liver transplantation is the only way forward.

THE WATERSHED

Presently the patient survival rates in India are comparable to the best centers in the world⁴. Over the last decade, 28 transplants have been

Table-3: Liver transplantation – Assessment details

Unfit	134
Neonatal cholestasis syndrome	104
Infection	74
Malnutrition	104
FHF	34
Ataxia	01
Sepsis	16
Multi organ failure	17

Table 4: Liver transplantations (1/10/97 to 24/10/08)

Fit for transplant	122
Refused (Girls 64, Boys 15)	79
Economic factor	70
Willing	51
Cadaver only	23
LRLT	28
Transplants performed	28*
Cadaver	02
LRLT	26
* One re-transplant	

Longest follow up 10 year

performed at our center. The year 2006 was water shed in terms of the learning curve being re written. We have recorded 100% survival rates in all fourteen pediatric liver transplants since then. The surgical expertise gained over the last few years combined with the advancements made and lessons learnt in the medical management have contributed in a big way to this achievement. Liver transplants in infants are now being performed with results comparable to those of children more than one year of age.

Despite these success stories, there is still a lack of awareness on existing liver transplant facilities in India even within the medical fraternity. It is the faith and support of the medical fraternity and the public at large that can help our endeavors to make LT a practically feasible and economically viable treatment modality in India.

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