Pediatric Liver Transplantation for Chronic Liver Disease

Introduction

Liver transplantation is indicated in end stage chronic liver disease.

The pediatric liver transplant evolved in the 1980s and became established in the 1990s. First successful pediatric liver transplant was performed in 1967 by Prof. Starlz. There were rapid advances in adult transplantation throughout the 1970s. 1986, when most adult units claimed a 1 year survival rate of 80% average 1 year survival rates in children were only 60% (1). Since then, there have been considerable advances in both medical and surgical management, with international 1 year survival rates from pediatric liver transplant in excess of 90% and 5-10 year survival rates of 80% (2). The success of this complex procedure has led to a significant increase in the number of children undergoing liver transplant world wide and has radically changed the prognosis of many babies and children dying of end-stage liver failure.

In India, however, the liver transplant programme picked up only in 2000’s and gradually gained momentum. The growth has been very slow initially, as is expected in any new programme. However over the last few years there has been a rapid growth in liver transplantation and at Sir Ganga Ram Hospital, Delhi more than 330 liver transplants have been carried till 2008 with >130 liver transplants in year 2008, thus making it the among the top 3 living related liver transplant centre in the world. However, the pediatric liver transplants have been 10% of the total transplants carried. Besides them, there are several other centres in India performing liver transplant such as Apollo Hospital Delhi, Global Hospital Hyderabd. It is now well realized now that the infrastructure and expertise is available in our country, and the confidence of the referring doctors and patients is gradually building up. Economic burden is however, a major set up in India.

Etiology of Chronic liver disease

End stage chronic liver disease / chronic liver failure could be secondary to cholestatic liver disease, metabolic liver disease or chronic hepatitis. The underlying causes under this groups are given in table - 1

(A) Cholestatic liver disease

Cholestatic liver disease is the commonest indication of liver transplantation in children. Of the Cholestatic liver disease, biliary atresia remains the main indication worldwide. Neonatal Cholestasis contributes to nearly 30% of the chronic liver disease in children in India and ~ 30%-35% of neonatal cholestasis cases are of biliary atresia. One of the major problems in our country is that there is a significant delay in the referral of these patients to tertiary referral centre and therefore, patients rarely benefit from a palliative Kasia’s portoenterostomy. It is, therefore, emphasized that patients with neonatal cholestasis must be urgently investigated to rule out underlying biliary atresia.

Box 1 : Common Causes of Chronic Liver failure requiring liver transplantation
(B) Metabolic liver disease

The common metabolic liver diseases in children for which liver transplant is indicated in west are α1-antitrypsin, tyrosinemia type I, Wilson’s disease, cystic fibrosis, glycogen storage type IV.

In India the commonest metabolic liver disease seen is Wilson’s disease. Wilson’s disease is rare autosomal recessive disorder of copper metabolism resulting in excessive accumulation of copper in liver, CNS, kidneys, cornea, skeletal system & other organs. The prevalence of the disorder is 1 in 30,000 worldwide with a carrier frequency of 1 person in 90. Early diagnosis & therapy with pencillamine / trientene should be curative but many children will present with established cirrhosis or fulminant liver failure.

Indications for liver transplantation in Wilson’s disease include cirrhosis with decompensation, progression of hepatic dysfunction despite treatment, exacerbation after discontinuation of therapy, fulminant hepatic failure and progressive and irreversible neurologic disease.

In fact in our small experience of liver transplants in children, 3 patients of Wilson's disease have undergone liver transplantation, one had presented with acute liver failure and the other two were chronic decompensated liver disease not responding to chelation therapy. Mean follow up is 22.6 months (8-33months) and they are all doing well post liver transplant.

Tyrosenemia type I is an autosomal recessive disorder of tyrosine metabolism, with a clinical presentation that includes both acute and chronic liver disease and multiorgan failure with cardiac, renal, and neurologic involvement. The management of this disorder has changed dramatically since the introduction of 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexenedione (NTBC), which prevents the formation of toxic metabolites and produces rapid clinical and biochemical improvement. Liver transplant is now indicated
only for those children who have a poor quality of life, do not respond to NTBC or in whom hepatic malignancy is thought to have developed (3). We have performed living related liver transplantation in one case of tyrosinemia with cirrhosis and dysplastic nodules.

Liver transplant in Cystic fibrosis is indicated if there evidence of hepatic decompensation. Fortunately incidence of cystic fibrosis is much less in India as compared to West though it definitely exists.

In Glycogen storage disease type I transplant is indicated only for children who develop multiple hepatic adenomas or in whom metabolic control has affected the quality of life. Children with glycogen storage disease types III and IV are more likely to progress to cirrhosis with portal hypertension and require transplant because of hepatic dysfunction.

(C) Chronic Hepatitis

Autoimmune Liver Disease Type I and II: Liver transplant is indicated for those children who have not responded to immunosuppression despite alternative therapy such as cyclosporine A, mycophenolate mofetil, or tacrolimus and those children who present with fulminant hepatic failure (4). Fulminant hepatic failure is more likely in children with type II autoimmune hepatitis (LKM1 positive), who have a worse prognosis and an increased requirement for liver transplant.

Chronic Hepatitis B & C: Although chronic hepatitis B or C is a major indication for transplant in adults, it is less common in children, many of whom will not develop symptomatic liver disease in childhood. Recurrence of hepatitis B or C is likely in 90% of patients transplanted for chronic disease but not for fulminant hepatitis. Prevention or recurrence of hepatitis B is less likely with prophylactic treatment of hepatitis B immunoglobulin and/or lamivudine.

(D) Cryptogenic Cirrhosis

The term 'cryptogenic cirrhosis' is used when despite all investigations the underlying causes of cirrhosis cannot be identified.

(E) Fibropolycystic Liver Disease

Liver transplant is indicated for those children in whom hepatic decompensation occurs secondary to recurrent cholangitis or portal hypertension or if hepatic enlargement affects the quality of life. Because the disease may be associated with infantile polycystic kidney disease in some children, both liver and kidney replacement may be required. (5)

(F) Primary Immunodeficiency

In this group of children, it is important to consider bone marrow transplant before the development of significant liver disease or to consider combined liver and bone marrow transplant if necessary. (6)
Primary Indications of Liver Transplantation in children in West

n= 3, 998 pediatric patients, adapted from the European Liver Transplantation Registry, 2002

Criteria for listing for liver transplantation in chronic liver disease

The major functions of the liver are (a) synthetic functions (b) formation and excretion of bile, (c) metabolic functions like glucose homeostasis and metabolism of nitrogenous wastes and drugs, (d) immunological functions and(e) hemodynamic functions. Any patient with chronic liver disease who has clinically significant abnormalities in 2 or more areas will likely be benefited from liver transplantation.

Timing of transplant for Chronic Liver Failure

The timing of liver transplantation for children with chronic liver failure may be difficult. It must be remembered that a patient of chronic liver disease must be referred early to a liver transplant centre so that optimum timing for transplant can be decided before the complications of liver disease adversely impair the quality of child’s life and before growth & development are irreversibly retarded. There are certain parameters which are taken as a guide for listing for liver transplantation

Lab Parameters: The most useful guide to the timing of liver transplant is provided by a variety of parameters that include

- a persistent rise in total bilirubin > 150 µmol/L (> 9 mg/dL),
- prolongation of the prothrombin ratio international normalized ratio [INR] > 1.4), and
- a persistent fall in serum albumin to < 35 g/L.(7) Serial evaluation of nutritional parameters is a useful guide to early hepatic decompensation

Clinical Parameters - (A) Nutritional Assessment: Among the clinical parameter, one of the most important indicator for liver transplantation is nutritional assessment. Serial evaluation of nutritional parameters is a useful guide to early hepatic decompensation. Progressive reduction of fat stores (measured by triceps skinfold or subscapular skinfold) or protein stores (measured by midarm circumference or midarm muscle area) despite intensive nutritional support is a good guide to hepatic decompensation.(8) Recently, the development of the PELD Score (PELD = pediatric end-stage liver disease) has confirmed these observations.(9)
Psychosocial development: Children with chronic liver disease may have both social and motor developmental delays that increase with time unless reversed following early liver transplant (10,11,12).

Hepatic complications: Children with severe hepatic complications such as chronic hepatic encephalopathy, refractory ascites, intractable pruritus and recurrent variceal bleeding despite medical management should be referred immediately for transplant. In some patients hepatopulmonary syndrome develops secondary to pulmonary shunting and this is an important indication for liver transplantation. The clinical score used in chronic liver disease are child Pugh score and PELD score.

Contraindications For Liver Transplant

With increasing experience, there are fewer contraindications to transplant. Although historically considered difficult, age < 1 year and size < 10 kg are no longer contraindications for transplant. Portal vein thrombosis increases the technical risk of the surgery, but it can now be managed with venous or prosthetic grafts. In our experience, we have operated on two biliary atresia with portal vein thrombosis and both are doing well. Vascular abnormalities such as the hypovascular syndrome are no longer considered contraindications. Although infection with human immunodeficiency virus (HIV) was a contraindication, the improvement in long-term prognosis with antiviral drugs means that this disease can be controlled before transplant. The following contraindications remain:

1. **Severe systemic sepsis** (in particular, fungal sepsis) at the time of operation. It is important that the operation be deferred until the infection has been appropriately treated.
2. **Malignant hepatic tumors with confirmed extrahepatic metastases.** (13)
3. **Severe extrahepatic disease** that is not considered reversible following liver transplant. This includes severe cardiopulmonary disease for which there is no possibility of corrective surgery or severe structural brain damage with a poor prognosis.
4. **Multiorgan failure**, especially owing to mitochondrial cytopathy, (14) because it has been shown that unless the mitochondrial defect is confined to the liver, liver transplant is not curative.
5. In the **respiratory chain defects** like Alper’s disease liver transplantation is contraindicated because of the progression of neurodegeneration despite transplant.
6. **Autoimmune and hemolytic anemia** in association with giant cell hepatitis is a rare and fatal disease in which there is a 100% recurrence rate post-transplant, and transplant is not recommended.

Recurrent disease: Hepatitis B and C have a recurrence rate of 90 to 100% post-transplant but can now be treated with antiviral agents before and after transplant. Autoimmune liver disease recurs in 24% of cases, as does primary sclerosing cholangitis. Although liver transplant is not contraindicated for these conditions, the rate of recurrence must form part of the counseling of families.

Pre Transplant Evaluation

The pre transplantation evaluation of the patient is particularly important and should include the following:

- Assessment of the severity of the liver disease and the possibility for medical management
- Assessment of the technical feasibility of the operation
- Consideration of any contraindications
- Psychological preparation of the family and child

The assessment has been tabulated in Box no.2.
Pretransplant assessment

Nutritional status
- Height, weight, triceps skinfold, midarm muscle area, midarm circumference

Identification of hepatic complications
- Ascites, varices

Cardiac assessment
- Electrocardiography, echocardiography, chest radiography, cardiac catheterization

Respiratory function
- Oxygen saturation,* ventilation-perfusion scan, lung function tests

Neurologic and developmental assessment
- Electroencephalography, Bailey developmental scales, Stanford-Binet intelligence scales

Renal function
- Urea, creatinine, electrolytes, urinary protein-to-creatinine ratio, chromium EDTA

Serology
- Cytomegalovirus; Epstein-Barr virus; varicella-zoster virus; herpes simplex virus; hepatitis A, B, and C; HIV; measles

Hematology
- Full blood count, platelets, blood group

Radiology
- Ultrasonography of liver and spleen for vascular anatomy, wrist radiography for bone age and rickets

Dental assessment

Preparations for liver transplantation

Immunizations

Most units consider live vaccines to be contraindicated after liver transplant because of the risk of dissemination secondary to immunosuppression. It is therefore better to complete normal immunizations before transplant.

Management of hepatic complications

It is important to ensure that specific hepatic complications are appropriately managed while the patient waits for transplant.

Recurrent variceal bleeding should be managed preferably with esophageal varix ligation than sclerotherapy. Intractable variceal bleeding may require the insertion of a transjugular intrahepatic portal systemic shunt. (15)

Sepsis that includes ascending cholangitis and spontaneous bacterial peritonitis should be treated with broad-spectrum antibiotics, whereas in children awaiting transplant for acute liver failure, prophylactic antifungal therapy is essential.

Ascites should be managed with diuretics and restriction of salt. Intervention with hemodialysis and hemofiltration should be considered if acute renal failure or hepatorenal failure develops. (16)
**Nutritional support**

It has been demonstrated with several studies indication that nutritional status at liver transplant is an important prognostic factor in survival. (17, 18). A high – calorie protein feed (150 to 200% estimated average requirement) is required with high calorie supplements are given orally or by nocturnal nasogastric enteral feeding or continuous enteral feeding.

**Psychological Preparation**

Liver transplant is a major undertaking for the child and family; thus, psychological counseling, information giving, and preparation of the child and family are paramount using a skilled multidisciplinary team with play therapists, psychologists, and schoolteachers.

**Liver transplant surgery**

The graft is a either cadaveric liver or a living related.

In **Cadaveric liver transplantation** the liver of a brain dead person is used for transplantation. Cadaveric transplants could be:

- **Whole graft**: The entire graft is transplanted in the recipient.
- **Reduced graft**: When only a part of the cadaveric liver (i.e. right/ left/left lateral part) is used for the recipient
- **Split graft**: The shortage of suitable organs for young children led to development of split livers. The liver of the cadaveric donor is divided and used for two patients usually the right lobe for adults and left lobe for children.

**Living related liver transplantation**: This has been a further step to answer the shortage of organs for children. In living related liver transplantation, a part of the liver from a living related donor is used in the child. This procedure is more popular in Eastern countries like Japan and Korea where cadaveric liver transplantation has not been possible until recently. To carry out living related liver transplants, 2 transplant surgeons team is required as simultaneously surgery is being carried out on the donor and recipient.

**Auxiliary liver transplant**: The term auxiliary liver transplant is referred when a part of the donor liver (usually segments 2+3) is implanted beside or in continuity with the native liver. The main purpose of this form of liver transplant is to ensure that the native liver is retained in the event of graft failure or for the future development of gene therapy. Auxiliary transplant is now accepted therapy for Crigler-Najjar syndrome type I (19) and also for propionicacidemia and ornithine transcarbamalase deficiency.(20)

The role of auxiliary liver transplant in the management of fulminant hepatic failure is more controversial. The rationale for using this technique in this condition is that, with time, the native liver may regenerate. Two recent studies in adults demonstrated that the native liver regenerates in approximately half of the patients. (21, 22)

In India cadaveric organ donation is next to negligible. Of all the liver transplants carried out in the country <5% have been cadaveric liver transplants and similarly our centre’s experience has been <5%.
Immunosuppression

Following liver transplant the patient requires immunosuppression usually for life long according to the present consensus. The various immunosuppressive drugs used following liver transplantation are cyclosporine, tacrolimus, mycophenolate mofetil and steroids. Newer drugs like OKT3, sirolimus and basiliximab are used in occasional patients.

Postoperative complications

**Early postoperative complications**

a) **Primary graft nonfunction**: Primary nonfunctioning of the transplanted liver occurs within 48 hours. The cause is unknown and may be related to donor factor. The only appropriate management is retransplant.

b) **Surgical complications of intra-abdominal hemorrhage**

c) **Vascular thrombosis, and venous outflow obstruction.**

   Hepatic artery thrombosis occurs in approximately 10% of pediatric liver grafts, and its frequency has decreased considerably following the introduction of reduction hepatectomy or living related transplant because of the increased size of the donor vessel. (23)

   Portal vein thrombosis is less common complication.

d) **Rejection**: Acute cellular rejection may occur between 7 and 10 days postoperatively. The incidence of acute rejection varies. It is less common in infants (20%) but increases to 50 to 60% in older children and adults. (24, 25).

   In majority of the cases it responds with increase in immunosuppression and high dose of steroids. It has been shown the acute rejection does not affect the long term outcome.

e) **Biliary complications**

   These include biliary leaks and structures and is usually managed by interventional radiology with requirement of surgical reconstruction is only few cases.

f) **Sepsis**

   Infection is still the most common complication following liver transplant (10,26). Bacterial infections are most common immediately after transplant and are related to the high doses of immunosuppressive drugs and central line infections. The mortality of patients with systemic infection is high but improved with new agents such as quinupristin and linezolide.

Late complications post transplant

These fall into two general categories: (1) Complication related to allograft itself and (2) those related to immunosuppressive drugs. They include chronic rejection, CMV and EBV infection, late biliary strictures, hepatic artery or portal vein thrombosis, post – transplant lymphoproliferative disease (PTLD), De nova autoimmune hepatitis, Nephrotoxicity and hyperlipidemia secondary to immunosuppressive drugs. Other side effects of immunosuppressive drugs include like hypertension, Hirsuitism, etc.

Scenario in India

It's heartening to see that liver transplantation programme in India has at last picked up. It has been slow to start with but the pace in the last couple of years has been better though we still have a long way to go ahead. There are several centres in the country which are now doing liver transplantation but there are only a couple of centres that have done >50 liver transplants. The adult numbers are far more than the pediatric numbers which account to only 10% of the total transplants in India. There are multiple reasons for this but
the most common reason is that the family finds it hard to spend a lot of money on a child. In the author’s centre experience, people are more willing to spend money on elderly people than infants and young children. Besides that bias of a girl child, cannot be less emphasized.

One of the major problems that we are facing in the country is lack of cadaveric donation - therefore, most of the transplants whether renal or liver carried out are living related. The human organ donation act was passed in 1984 in India. The donor has to be spouse or first degree relative or emotionally related to the patient. The importance and safety of cadaveric liver transplantation cannot be undermined and I think we must all work in the direction of promoting cadaveric organ donation in our country to benefit several people from various organs. In fact following the promotion of cadaveric organ donation there will be significant impetus in the liver transplant programme in the country.

Author’s Centre Experience

Our centre, Sir Ganga Ram Hospital, Delhi is the largest centre of liver transplantation in India where presently 4-6 liver transplants are carried out monthly. In fact in the year 2006, >65 liver transplants have been carried out and thus it has become South Asia’s largest living related liver transplant centre having completed >110 liver transplants. They are mostly living related liver transplants due to the shortage of cadaveric organs as mentioned earlier.

So far we have performed eleven pediatric liver transplants with a 100% success or survival rate. Mean age of follow up is 14.8 months (1-40 months) with the first case now being 3½ years post liver transplant. Indications for liver transplantation have been Wilson’s disease –3, biliary atresia –3, and 1 each of progressive familial intrahepatic cholestasis, tyrosinemia, cryptogenic liver cirrhosis, hepatitis A induced liver failure and hemangioendothelioma.

Box - 4: - Some photographs of the liver transplant patients operated at Sir Ganga Ram Hospital.

Outcome

Outcome of Pediatric liver transplantation has shown incremental improvements from the 1980s to late 1990s. Studies of pediatric liver transplantation (SPLIT) registry, which was initiated in 1995, gives an overview of the results of pediatric liver transplantation achievable in the last 7 years. Of 1092 pediatric liver transplanted children, the Kaplan – Meier probability of patient survival at 1 and 3 years was 86.3% and 83.3%, respectively, with corresponding graft survival rates of 80.2% and 75.3% respectively.
The Kyoto series, the largest in the world, is driven by virtually nonexistent cadaveric supply i.e. based on living related transplantation. The Kyoto series shows excellent and comparable patient and graft survival rates, 81% and 79% at 5 years, to the overall results of cadaveric pediatric liver transplantation. In another large series, Reding et al. reported a 7 year experience with living donor transplants in children, which showed 1 and 5 years survival rates of 92% and 89% for patient and graft 90% and 86% for graft, respectively. Although biliary complications may be more common in living donor compared with whole organ transplants, these usually do not impact on patient or graft survival.

**Quality of life**

It is now anticipated that children who survive liver transplant will achieve a normal lifestyle despite the necessity for continuous monitoring of immunosuppressive treatment. Children transplanted for certain metabolic liver disease, tyrosinemia type –1 may have both phenotypic and function recovery. Children with Crigler-Najjar syndrome type 1 have functional recovery of enzyme activity.

An important aspect of long term survival is the development of puberty. A long term study from France has demonstrated that there are no differences between the genders in attaining puberty and developing secondary sexual characteristics (27). Girls develop menarche, and successful pregnancies have been reported for females receiving both cyclosporine and tacrolimus immunosuppression. (28)

**Summary**

Liver transplant for chronic liver failure is an effective therapy that restores good quality of life to over 80% of recipients. Considerable advances in medical and surgical expertise and immunosuppression have improved not only survival but also quality of life for the majority of liver transplant recipients. It is hoped that advances in molecular genetics will lead to effective gene therapy or hepatocyte transplant (29, 30) In India, both the infrastructure and expertise for liver transplantation is available and it has at last picked up, but the growth of transplant programme is still far from desirable. In the West the rate of liver transplants is 12 – 15/ million while in India its 0.08/million presently.
References:


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