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Pediatric Liver Transplantation- A Beacon of Hope

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Introduction

Liver transplantation is an accepted therapy for end stage disease and fulminant hepatic failure. One-year survival has progressively increased to nearly 90% in patients transplanted for most forms of liver disease. Parallel advances in organ procurement, operative technique, use of safe and potent immunosuppressive drugs, and infection control are responsible for improved patient survival. The history of pediatric liver transplantation has clearly shown that success is dependent on strict and integrated multidisciplinary collaboration [1] among pediatricians, pediatric transplant hepatologists, transplant surgeons, nurses, transplant coordinators, psychologists and social workers.

Liver transplantation was first attempted in dogs by Welch in Albany in 1955 and Cannon in California in 1956. The first ever human liver transplantation in the world was performed on March1st, 1963 by Thomas E Starzl in Denver, University of Colorado Health Sciences Center (UCHSC). The recipient was a 3 year old child with Biliary Atresia (Donor - Child who died from brain tumor).The child, however, succumbed to death due to uncontrolled hemorrhage [4]. The first long term survival was achieved in 1967 by Starzl in Denver, Colorado, USA. In July 1967, a two and a half year old child underwent orthotopic liver transplantation. Despite the developments in surgical techniques, liver transplantation remained experimental till 1970 with 1 year patient survival rate around 25%.

Thomas E Starzl's pioneering efforts in organ transplantation for four decades have resulted in clinically proven treatments for patients with end – staged organ failure, who were previously doomed to death [12]. His contributions to immunosuppression, organ procurement, organ preservation, tissue matching, surgical transplant technology and the team approach to organ transplantation paved the way for the acceptance of heart, lung, pancreas, intestinal, liver and kidney transplantation. He also introduced the first major innovation in hypothermia, when canine liver allografts were cooled by infusion of chilled fluids into the vascular bed of hepatic allografts via the portal vein. Meanwhile Sir Roy Yorke Calne introduced cyclosporine, and accomplished the first liver transplantation in Europe and the World's first combined heart, lung and liver transplantation [2].

Indications

Liver transplantation is usually performed in patients with progressive liver disease with the expectation of liver failure, stable liver disease with known outcome of significant mortality and morbidity, hepatic based metabolic disease, fulminant hepatic failure or primary localized malignancy [3]. Patients who have Acute Liver Failure can recover spontaneously, but those who have sub fulminant hepatic failures have 100% mortality without transplantation [2].

Acute Liver Failure

1. **Acute hepatitis:** HAV, HBV and HEV (less common).
2. **Hepatotoxic Drugs/ toxins:** Acetaminophen, Amanita phylloides, Halothane.
3. **Cholestatic conditions:** Extrahepatic biliary atresia, progressive familial intrahepatic cholestasis type 1, 2 and 3, Alagille syndrome, Sclerosing cholangitis, Total parenteral nutrition associated with cholestasis, Idiopathic cholestasis.
4. **Chronic Liver Disease with cirrhosis:** Chronic HBV/HCV, Autoimmune hepatitis, biliary cirrhosis, primary sclerosing cholangitis, cryptogenic liver disease.
5. **Metabolic disorders:** Wilson's disease, Hereditary hemochromatosis; Alpha-1 antitrypsin deficiency, familial hypercholesterolemia, Tyrosinemia, Crigler-Najjar disease type I.
6. **Malignancy**: Primary malignancy (Hepatocellular carcinoma, cholangiocarcinoma); Secondary malignancy (Carcinoids, islet cell tumors).

7. **Veno-occlusive disease**: Budd-Chiari syndrome.
8. **Miscellaneous:** Polycystic liver disease, trauma, cystic fibrosis, congenital hepatic fibrosis.
9. **Retransplantation.**

Contraindications

Contraindications to liver transplantation include poor compliance, lack of an adequate support system, and clinical conditions associated with poor transplantation outcome. Some contraindications are absolute and others are relative.

Absolute

Coma with irreversible brain injury, Extra hepatic malignancy, Active uncontrolled infections/sepsis, active alcohol or drug abuse, Severe cardiopulmonary disease, Advanced liver disease with more than one organ failure, AIDS, Life threatening systemic disease [2].

Relative

Age less than 2 years and more than 70 years, Renal failure, Prior portacaval shunt, Portal vein thrombosis, Prior complex hepato-biliary surgery, Re- transplant, HIV, Serum creatinine >2mg/dl, Cytomegalovirus mismatch and advanced liver disease [5].

Types of Transplant

Persistent shortage of donors and increase in the number of patients on waiting have forced the transplantation units to lead a search for alternative methods to expand the donor pool, such as living donor, split liver and sequential (Domino) transplantation [5]. It includes.

1. Segmental (Split) Liver Transplantation (SLT): It's a surgical technique that creates two allografts. It can be either Cadaveric split transplantation or living related split transplantation. Split liver transplantation was simultaneously reported by Pichlmayr and Bismuth in 1989.

2. Auxiliary Partial Orthotopic Liver Transplantation (APOLT): It was proposed for the treatment of acute liver failure in 1956 by Godrich. Partial native liver resection is done to make room in the right hypochondrium to transplant an auxiliary partial liver in the orthotopic position. The auxiliary graft supports the remnant native liver during regeneration and when it recovers, the graft can be abandoned or removed and the patient can be freed from immunosuppressant.

3. Domino Liver Transplantation (Domino LTX): Domino liver transplantation was introduced in the year 1977. In this, a patient with metabolic liver disease is transplanted from a deceased or living donor liver, but the explanted liver with metabolic liver disease of the first recipient is used for transplanting in another patient (second recipient, called domino recipient) with End Stage Liver Disease. This liver can be transplanted to recipient who has given full consent.

Recent Advances in Liver Transplantation

Liver transplantation has significantly improved the prognosis in patients with End Stage Liver Disease [5]. The incidence of chronic liver failure is expected to increase over the next ten years as a result of the silent epidemic of hepatitis C. As a result of shortage of organ donors, new technology has emerged for the acute and long term support of patients with damaged liver. Recent developments as alternative options include:

Hepatocyte transplantation: Transplantation of human hepatocyte is being developed to treat metabolic liver disease where a supply of normally functioning liver cells can correct a genetic deficiency.

Xenotransplantation: Transplantation of living cells, tissues or organs from one species to another such as from pigs to humans. Such cells, tissues or organs are called xenografts or xenotransplants.

Stem cell transplantation: A stem cell is an undifferentiated cell capable of renewing itself throughout its life and of generating one or more types of differentiated cells. When embryonic stem cells are the only ones to be potential, adult tissues with high cellular turnover (eg: skin, gut mucosa and bone marrow) retain a population of stem cells with restricted differentiation potential that constantly supply the tissue with new cells. Circulating hematopoietic stem cells contribute to the repair of solid organs, like the liver, offering promise in the future.

Evaluation of Living Donor

Living organ donation is a complex decision for the donor and his or her family. Every potential donor has a freedom to withdraw himself from organ donation during the course of evaluation and reason for withdrawal should not be disclosed. An ideal donor should be mentally, physically and psychologically fit. He or she should volunteer for donation with no financial or any other benefits from donation and without any compulsion from the family members or medical fraternity for organ donation. It is preferred that a relative of the recipient be the donor. The donor should be aware of the morbidity, mortality and other consequences of organ donation [8]. The aim of donor evaluation is to find out whether donor is suitable for donation or not, as well as detect hidden medical diseases in him or her. There is also detailed anatomical evaluation of the liver related to segmental anatomy, vascular anatomy, estimate the required graft volume all to avoid unnecessary morbidity and mortality. One must also evaluate the psychological status, the motivation for donation and legal requirement. The major steps in the evaluation include:

Step I: History (HTN, IHD, DM, COPD, Malignancy, Asthma; Intake of drugs, alcohol, females -pregnancy) Physical examination (Body weight, body height, body mass index, body surface area, pulse rate) Hematology (Hb, PCV, MCV, MCHC, PT, APTT, INR, ABO blood typing)Biochemical (AST, ALT, RFT, LFT, Lipid profile, Metabolic (Blood sugar- fasting, postprandial) Serology (HBsAg, HBeAg, Anti HCV Ab, CMV, EBV, VDRL, HIV).

Others- Ceruloplasmin, ferritin, transferring, antinuclear antibody, tumor markers (AFP, CEA).

Step II: Psychological assessment: Ultrasound, Chest X-ray, ABG, ECG, Echo, CT, MRI).

Step III: Liver Biopsy (in selected cases of fatty liver).

Step IV: Lymph cytotoxic antibody screening, HLA typing and cross matching, informed consent from donor, recipient and relatives.

Preoperative Evaluation

Assessment

Patient preparation and proper timing of transplantation are as important as the surgery [6]. Liver transplant should be considered for any child with end stage liver disease with a predicted survival of less than one year. Assessment includes thorough nutritional, developmental, cardiac and dental evaluation. Hepatic function, serological examination and histocompatability of the donor liver cells with the recipient are also checked along with the vascular anatomy of the liver.

Pediatric Recipient Evaluation and Assessment:

Disease Specific

Autoimmune diseases: Antinuclear antibody, IgG, Anti smooth muscle antibody, Liver& kidney microsomal antibody, Anti neutrophil cytoplasmic antibody

Wilson's disease: Serum ceruloplasmin level, 24hr urine copper.

Alpha 1 antitrypsin deficiency: Phenotyping

Neonatal hemochromatosis: Serum ferritin, transferrin levels, iron studies, MRI of pancreas

HBV: HBsAg, HBeAg, Anti HBs Ab, Anti HBc Ab, Anti HBe

HBV: DNA, mutations in HBV

HCV: HCV RNA, Genotyping

CMV/EBV screening: Age > 1 year (IgG&IgMtitre)

Autoimmune Diseases: Antinuclear antibody, IgG, Antismooth muscle antibody

Tumor Markers: Alpha-fetoprotein, Carcinoembryogenic antigen, CA 19-9

Hemochromatosis: Serum ferritin, transferrin, salivary gland biopsy

Other Standard Tests: Abdominal ultrasound with Doppler, ECG, PFT, Endoscopic evaluations

Preparation for Liver Transplantation

The important aspects of the preparation are

a. Nutritional rehabilitation: Preoperative nutritional status is an important factor affecting outcome following liver transplant.

b. Immunization: It is essential to make sure that routine immunizations are complete. If necessary, immunization for MMR and varicella should also be done.

c. 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 trans-jugular intrahepatic portal shunt. Hepatic encephalopathy is treated by low sodium diet and oral lactulose.

d. Counseling: Education and counseling of the family and the child is of paramount importance to sustain them through the stressful procedure, the prolonged postoperative period and the lifelong immunosuppressive therapy with its risks and side effects [6].

Surgical Procedure [9]

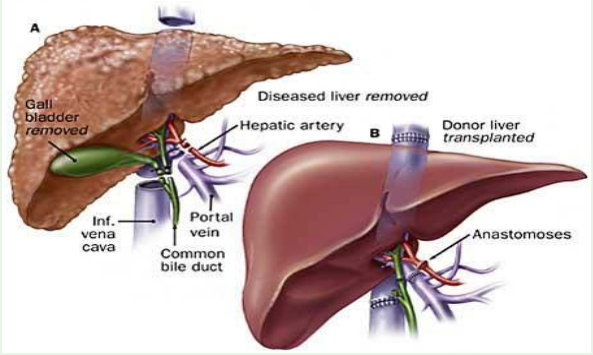

Figure 1: A. Diseased liver and B. Donor liver.

Post Operative Care

The early postoperative period consists of managing problems related to technical complications and to the prevention, diagnosis, and treatment of acute rejection and infection. In order to avoid rejection of the graft, immunosuppressive drugs must be administered. Some of the commonly used drugs are corticosteroids and calcineurin inhibitors.

Complications

a. Primary Non Function (PNF): It is defined as primary graft failure that resulted in death or retransplantation within 30 days of the primary transplantation. The incidence of PNF among liver recipients is 2 – 14%. The precise cause of PNF is unknown.

b. Allograft Rejection: It is defined as "an immunological reaction to the presence of a foreign tissue or organ, which has the potential to result in graft dysfunction and failure. Hepatic allograft rejection is divided into hyper acute (antibody mediated) rejection, Acute cellular rejection, Chronic (ductopenic) rejection. Young age of the recipient, donor age > 35 years, high AST levels, few HLA-DR matches are some of the risk factors for acute cellular rejection.

c. Biliary Complications: Biliary strictures and bile leaks are the most common biliary complications following transplantation and the incidence of biliary tract complication after orthotopic liver transplantation varies from 11%-25%. Potential sources for biliary complications are technical, anatomical, ischemic and immunological factors including arterial injury.

d. Vascular Complications: Portal vein complications and arterial complications are the major vascular complications. The portal vein complications include portal vein stenosis, portal vein thrombosis, and late portal vein aneurysm after transplantation. Obstruction of the portal vein and outflow veins may also have deleterious consequences, including ascites, abdominal distension, liver enzyme elevation and gastrointestinal bleeding. Arterial complications after orthotopic liver transplantation vary from 2% – 25%. Various complications are hepatic artery thrombosis, stenosis, pseudo-aneurysm, rupture, and arterial steal syndrome. Hepatic artery thrombosis is the most frequent vascular complications and is associated with high morbidity and mortality.

e. Post-Transplant Infections: Infections in solid organ transplants contribute to a significant morbidity and mortality. Infections can be early infections and late infections. Early infections are the infections in the first six months after transplantation. These infections are mostly related to transplant surgery and wound related in the early post-transplant period, followed by bacterial, viral and fungal infections. The late infections are those occurring after six months after transplantation. Opportunistic infections are less common after six months of post-transplant period. The major types of infections are Abdominal infections (wound related infections, bilomas); pulmonary infections; CNS infections; bacterial infections (mycobacterium tuberculosis, listeria monocytogenes); viral infections (CMV, EBV, HBV, HCV, HIV, HSV); fungal infections (candidiasis, aspergillus, Cryptococcus, pneumocystis carinii) and protozoa (Toxoplasma Gondii).

f. Respiratory Complications: Pulmonary edema [7]

g. Cardiomyopathies, Hemochromatosis; CNS hemorrhage; Seizures.

h. DIC, Thrombocytopenia; Diabetes Mellitus.

Conclusion

Pediatric liver transplant is an evolving, yet challenging aspect in the management of end stage liver disease in the pediatric population. It provides a ray of hope to the child and family and opportunity to live a long and healthy life. Health professionals play a crucial role during the course of stay in hospital.

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