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CURRENT TOPIC

Liver transplantation

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Orthotopic liver transplantation (OLT) is a therapeutic option that should be considered at an early stage in any child with a life threatening liver disease.[1] The majority of recipients can expect to enjoy a good quality life with normal growth and development.[2] Liver transplantation should be performed before growth is retarded by liver disease.[3] The results are better, however, in children transplanted after 1 year of age or when weighing more than 10 kg.[3 4] The procedure is best done electively rather than as an emergency.[5]

Since the National Institutes of Health Consensus Development Conference concluded in 1983 that liver transplantation was an effective therapy for end stage liver disease,[6] liver transplantation has gradually become available to more and more children. Over 1000 children had received liver grafts in the USA by 1990,[5] while by 1992 over 500 livers have been grafted into children aged less than 13 years in Europe; 50% were less than 3 years of age. Over 270 children, aged 16 or less, were transplanted by January 1992 in three British centres. Since 1983 the immediate outcome from transplantation has gradually improved because of developments in operative techniques, intensive care, immunosuppression, better prevention and control of infection, and earlier retransplantation when the first graft fails.[5 7] In the Cambridge/King's College Hospital liver transplantation programme, analysis of the first 100 children transplanted between December 1983 and March 1990[8] gave an overall survival rate of 65% but in the last two years the one year survival rate was 86%; five year survival rates ranging from 64 to 78% have been reported.[3 5 7] Even in infants under 12 months of age, one year survival figures of 65% have been achieved, although with considerable morbidity.[4] The use of reduction hepatectomy, in which a part of the right or left lobe from an older child or even an adult is used to replace the diseased liver, has decreased the chances of death while waiting for a donor of similar size and blood group.[9] In North America segmental grafts from living relatives have had a similar effect and given survival rates of 90% in infants in whom portoenterostomy for biliary atresia had been unsuccessful.[10]

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Constraints

There are certain limitations which curb the use of this powerful therapy. Even in the best circumstances between 10% and 15% die within three months of grafting.[3 5 7–9] Removing and replacing a diseased liver is a demanding surgical procedure. The bile duct, hepatic artery, portal vein and hepatic veins, or inferior vena cava, require careful anastomosis to the appropriate host structures. Even more skill is required if only part of a liver is used.[9] A period of intensive care follows during which potentially lethal complications are common.[8 11–13]

Immunosuppression is achieved with cyclosporin, azathioprine and corticosteroids, the latter in relatively large doses initially when rejection is most severe. In the early weeks there is a very slender margin of safety between giving too much immunosuppresive therapy with an enhanced risk of infection and other toxic effects and giving too little and incurring rejection. Distinguishing acute rejection, which requires increased doses of corticosteroids and/or anti-lymphocytic antibodies, from systemic infection (viral, bacterial, fungal and/or protozoal) and from major complications requiring surgical management such as bile duct obstruction, hepatic artery thrombosis and/or portal vein thrombosis, is a major challenge. Preventing chronic rejection which is heralded by an insidious deterioration of liver function is another major difficulty. A new immunosuppressant, FK506, which promises to reduce the risk of both acute and chronic rejection, is currently being evaluated.[14] Up to 40% of recipients require regrafting, mainly for chronic rejection, vascular thrombosis, or primary non-function.

The patient is at risk from longer term surgical complications, and medical problems associated with lifelong immunosuppression. Opportunistic infections and community acquired infections are always a danger.[15] A worrying complication is Epstein–Barr virus related lymphoproliferative disease, which is frequently fatal unless immunosuppressive drugs are stopped. In one paediatric series an incidence of over 2·8% per year was reported.[16] Deaths are rare between two and five years after OLT. The longer term prognosis remains unknown. The longest surviving recipient remains well more than 20 years after transplantation.[5]

Lack of donor livers matched for size, blood group, and cytomegalovirus (CMV) status remains a major difficulty particularly in those less than 2 years of age. Surgical advances including reduction hepatectomy and split liver grafting have helped, but have increased complication rates in the short term at least.[3 5] Another important limiting factor is scarcity of intensive care facilities and trained nursing staff.

Indications for liver transplantation and its timing

Initially OLT was undertaken mainly in children with chronic liver disease, but OLT now has an increasingly effective role in the management of selected children with fulminant liver failure. It has also been successful in some liver based metabolic disorders, in which liver function and structure are not primarily affected but in which irreparable damage to other vital organs can occur (table 1). Rarely it has been used for children with cholestatic disorders in whom the quality of life is severely impaired by pruritus or osteopenia, although liver damage is not advanced. It has a limited role in liver tumours which cannot be successfully treated by subtotal hepatectomy and cytotoxics.

The timing of liver transplantation is determined by consideration of the child's prospects with other forms of treatment, the anticipated availability of a donor and of transplant facilities, and the likely outcome of OLT. It is essential to confirm the primary diagnosis of the liver disease, to estimate its severity, and to be aware of its likely evolution with other forms of treatment. Comprehensive evaluation is essential in minimising adverse effects of the procedure on the child and family. The transplantation coordinator, nutritionist, psychologist, nurse specialist, and social worker are indispensable in this process.[17 18]

CHRONIC LIVER DISORDERS

Selecting the best time for surgery is difficult. A major problem in any form of cirrhosis is that the course may be punctuated by life threatening complications. If these are anticipated and treated effectively the child may remain well with normal growth and development for many years. If mismanaged the patient may die prematurely. Complications which warn that early assessment for transplantation is essential in any form of chronic liver disease are given in table 2. In particular disorders other features are of prognostic importance. If jaundice persists after portoenterostomy for biliary atresia, transplantation is indicated as soon as linear growth slows or at the earliest signs of complications of cirrhosis. Recurrence of jaundice in patients with α_1-antitrypsin deficiency (protease inhibitor phenotype ZZ) requires similarly urgent action.[20] Wilson's disease is fatal without transplantation in those presenting with fulminant liver failure and in 50% of those with cirrhosis. For those with cirrhosis a useful index distinguishes children who should be transplanted as soon as a donor becomes available from those who will survive with penicillamine therapy alone or with zinc sulphate.[21]

In the acute form of tyrosinaemia liver transplantation should be performed as soon as growth arrest occurs, usually around 5 months of age. For the more chronic form it should be undertaken if the metabolic complications cannot be controlled by diet and drug treatment or at the earliest suspicion of malignant change within the liver. By 3 years of age the risk of hepatocellular carcinoma is so high that elective transplantation must be considered if the liver is nodular on ultrasonic or computed tomographic scans.[22]

The results of liver transplantation in over 30 patients with cystic fibrosis with predominantly liver involvement appear to be as good as in other disorders with as yet no evidence that infective complications other than pseudomonas and aspergillosis are particular problems. Some recipients experience a significant improvement in pulmonary function.[5]

Although a rational plan can be developed for most children with chronic liver disease on the basis of current knowledge, a more sound scientific basis for estimating the risks with or without transplantation in the individual patient would be invaluable. Paediatric hepatology units in conjunction with referring paediatricians must develop a database which would allow more precise determination of the exact indications for transplantation. Referral as soon as the patient is identified as having a liver disorder requiring possible transplantation will help to achieve this. Equally important, early referral may assist by confirming the exact diagnosis, suggesting alternative treatment and help in managing complications.

Table 1 Liver transplantation for metabolic disorders

End stage liver disease or premalignant changes
α_1-Antitrypsin deficiency
Wilson's disease
Tyrosinaemia
Galactosaemia
Haemochromatosis
Glycogen storage disease type 4
Cystic fibrosis
Defects of fatty acid oxidation
Glycogen storage disease type 1
For major extrahepatic features
Familial hypercholesterolaemia
Primary hyperoxaluria
Crigler–Najjar syndrome
Factor VIII deficiency
Protein C deficiency
Tyrosinaemia
Urea cycle defects
Glycogen storage disease type 1

Table 2 Indications for liver transplantation in chronic liver disease

Ascites refractory to fluid restriction and diuretics
Alimentary bleeding not controlled by sclerotherapy or propranalol
Spontaneous bacterial peritonitis
Growth retardation
Hepatic encephalopathy
Hypoxia
Prothrombin ratio (INR) >1·4
Cholesterol <2·6 mmol/l (100 mg/100 ml)
Indirect bilirubin >102 μmol/l (6 mg/100 ml)
Poor MEGEX test result[19]

ACUTE LIVER FAILURE

Although acute liver failure is potentially reversible with full recovery, the mortality without transplantation is 90% if the international normalised prothrombin ratio (INR) is greater than 4·0 rising to 100% if over 6. The complications of this multisystem disorder, particularly cerebral oedema, renal failure and systemic infection, require meticulous intensive care and a ready supply of donors if transplantation is to be successful. Four of seven children with severe acute liver failure (INR> 4) transplanted between March 1988 and August 1991 at King's

College Hospital survive with a median follow up of 18 months.[23] Therefore any child with apparent acute liver disease and encephalopathy, or with an INR prothrombin ratio of greater than 1·6 which is not corrected by intravenous vitamin K, should be referred to a unit offering skilled intensive care and the possibility of early transplantation if indicated.

LIVER BASED METABOLIC DISORDERS

In liver based metabolic disorders associated with liver damage the indications for transplantation (table 1) are similar to those in any other form of cirrhosis except where mentioned in the text. The current indications for transplantation when the liver is structurally normal but the patient is at risk from irreparable damage to vital tissue (for example, the brain, heart, or kidneys), caused by a hepatic based defect in metabolism, has been the subject of recent reviews.[24 25] In two rapidly developing fields close liaison between hepatologists and specialists in metabolic disorders is mandatory. OLT has not been effective in erythropoietic protoporphyria and Niemann–Pick disease type II.

Contraindications

Contraindications for transplantation are in a state of flux as surgical and medical advances overcome particular problems. At present metastatic malignancy, intractable extrahepatic sepsis particularly fungal, and permanent neurological damage are considered contraindications. Relative contraindications include complex congenital heart disease, major intra-abdominal vascular anomalies, advanced renal or lung disease, and severe short bowel syndrome. The place of transplantation in patients with cirrhosis due to hepatitis B is controversial since the recurrence of viral infection, with a high incidence liver damage, cannot be reliably prevented. Its onset can be delayed by hyperimmune gammaglobulin. The position of liver transplantation in the patient who is positive for HIV is even more contentious.[5 7]

Improving the outcome of liver transplantation

The primary paediatrician can work with the hepatologist in minimising complications. Before transplantation a full programme of immunisation against viruses, *Streptococcus pneumoniae*, and *Haemophilus influenzae* should be instituted. Avoiding unnecessary hospitalisation and/or antimicrobials before transplantation will reduce the risk of colonisation by resistant organisms. Expert care of complications of cirrhosis such as bleeding varices and ascites will help to bring the patient to transplantation in better condition and minimise postoperative problems. Nutritional support in the form of calories, protein and vitamin supplements if necessary, given by nasogastric feeding and rarely intravenously, may allow the patient to tolerate transplantation more satisfactorily.[3 17] Every effort should be made to avoid intra-abdominal surgery in patients who are potential candidates. Surgery in the area of the porta hepatis causes particular difficulties. The parents, and as far as possible the child, should be fully informed of the likely course and possible problems so that they and the family can make the appropriate plans.

The remarkable wellbeing, restored energy, catch-up growth, good scholastic performance and social adjustment of survivors, many of whom were desperately ill while awaiting transplantation, should be a stimulus to further developments to bring the early mortality of this procedure down to that of more conventional surgical procedures. With the present rate of improvements in surgical techniques, donor organ preservation, immunosuppression, antimicrobial measures and supportive care, this seems a realistic goal in the next decade. For this to become possible in Britain or northern Europe it will be essential to expand intensive care facilities for children.

Paediatricians have a key role in the early recognition and referral of infants and children with life threatening acute and chronic liver disorders. With early referral, less hazardous treatment may be possible. Biliary atresia accounts for 50–70% of children transplanted in most centres.[3–5 8] In up to 70% of children portoenterostomy before 8 weeks of age delayed transplantation for up to 15 years, if not indefinitely.[26] The majority in Britian are still receiving surgery after 8 weeks of age because primary physicians and paediatricians fail to recognise that significant hepatobiliary disease is always present in any child with even a mild conjugated jaundice.[27] Early referral can be equally efficacious in other disorders. It also gives more time to minimise potential complications and gives a greater chance of finding a suitable donor. Scarcity of donors is still a major obstacle to optimising this therapy in infants and young children. Paediatricians and workers in the intensive care facilities must recognise that organ donation is a potentially positive step for some donors' families as well as being life saving for the recipient.

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Occult liver injury in child abuse

Abdominal injury in child abuse may be more common than is generally realised. Over a nine month period in 1989–90 doctors at the Children's Hospital in Buffalo, New York State (Pierre N Coant and colleagues, *Pediatrics* 1992;**89**:274–8) examined 50 children suspected of physical (non-sexual) abuse. One had clinical evidence of abdominal trauma but the remaining 49 had no suggestion of abdominal injury either from the history or on clinical examination. Serum activities of liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) were measured routinely and four of the 49 children had raised activities usually of all three enzymes, although in one patient only the AST was high. The four children with raised enzymes each had an abdominal computed tomogram and three of them were shown to have lacerations of the liver. All of them recovered without surgery. The enzyme activities returned to normal within 48 hours and the degree of increase was very variable (between twice and 100 times the upper limit of normal) possibly because of variation in the time from injury to presentation at the hospital.

Though these children recovered without treatment, it is clearly important to know about these injuries because not only do the children need careful observation to ensure that they recover without complication but the injuries are of themselves of great legal significance and the knowledge is important in planning future management. Most children with physical injuries suspected to be non-accidental have blood taken for a blood count and clotting screen; it seems reasonable to include a transaminase activity at the same time. The incidence of liver laceration in this series was 6% but some of the children (the authors do not say how many) did not suffer physical trauma but were examined because of suspicion. In children with definite physical injuries the incidence of liver trauma would presumably be higher.

It is interesting that the liver lacerations in this series were all to the left of the liver whereas accidental injury to the liver usually involves the right side. Clearly a right handed blow is likely to strike the left side of the liver if delivered from the front. Similarly splenic injury is said to be rare in child abuse, presumably because the spleen is protected by the rib cage from a right handed blow. The handedness of the alleged assailant might also be of legal significance.

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