Annotations

Organ transplantation for inherited metabolic disease

With the advent of successful immunosuppression and improved survival rates in the 1980s organ transplantation for inherited metabolic disease became a therapeutic reality. This review will specifically concentrate on progress with liver transplantation for metabolic disease.

The aim of liver transplantation in this clinical situation is to cure the inherited metabolic defect both phenotypically and functionally. It is indicated in children with inborn errors of metabolism due to a primary hepatic enzyme deficiency that leads to either liver disease and/or hepatic cancer, or severe extrahepatic disease, when complete resolution of the disease may be anticipated after transplantation.

Cure of these metabolic diseases may require liver transplantation alone, or in combination with kidney, heart, or bone marrow transplantation.1

Inherited metabolic disorders leading to hepatic disease

This group of disorders includes those diseases in which: (1) There is a specific hepatic enzyme deficiency that leads to acute or chronic liver failure and the potential development of hepatic cancer (α₂-antitrypsin deficiency, tyrosinaemia type I, or glycogen storage disease type IV). (2) The precise metabolic defect is unknown but the main clinical features are hepatic (Wilson's disease, Byler's disease, neonatal haemochromatosis). (3) The hepatic enzyme deficiency leads to acquired liver disease (factor VIII and IX deficiency and subsequent chronic viral hepatitis).

The indications for transplantation in the first group are thus related not only to the correction of the metabolic defect but to the severity of irreversible liver disease and the prevention of hepatic malignancy.

In diseases such as α₂-antitrypsin deficiency and Byler’s disease which have predominantly hepatic manifestations with no effective medical treatment, liver transplantation provides both a phenotypic and functional cure.2,3

Until recently, tyrosinaemia type I, in which the deficiency of the hepatic enzyme fumaryl-aceto-acetase leads to hepatic, renal, cardiac, and neurological disease, has been a common indication for liver replacement. There are many reports of how successful surgery has reversed the hepatic and extrahepatic manifestations of this disease despite persistent production of the toxic metabolite succinyl acetone by the kidneys.4,5 As hepatic carcinoma inevitably develops in these children interest has focused on early detection of malignancy using radiology6 and pathological screening7 and establishing the correct timing for transplantation. The recent discovery of a chemical (NTBC),8 which prevents the formation of toxic metabolites and reverses the clinical and biochemical manifestations of this disease may alter not only the natural history but the indications for liver transplantation.

In contrast, the main indication for transplantation in children with Wilson’s disease in which early penicillamine treatment may be effective, includes those who present with acute liver failure and those in whom penicillamine treatment is ineffective.9 The reversal of the underlying abnormal copper metabolism has been reported after transplantation, as has the disappearance of Kayser-Fleisher rings10 and neurological disease.11

Neonatal haemochromatosis, which is a rare autosomal recessive disorder that presents with acute liver failure in the first six weeks of life, is a recent indication for liver transplantation. Before the successful development of reduction hepatectomy and improvements in technical expertise these children were considered too young and sick to be considered for liver replacement. Recent reports indicate complete resolution of the disease and good long term survival after transplantation.12

Adequate medical treatment should prevent the need for liver transplantation in galactosaemia13 or glycogen storage disease, although the development of cirrhosis in glycogen storage disease type IV may be an indication.14

In diseases with multiorgan failure, such as cystic fibrosis and protoporphyria, liver replacement may reverse the hepatic complications but has no influence on the extrahepatic manifestations15,16 and considerable care is required in selection of recipients. In children with severe cystic fibrosis lung and liver disease, a heart/lung/liver transplant may be indicated.

Finally, liver transplantation may be indicated for chronic viral hepatitis acquired with treatment for inherited disorders of haemostasis such as factor VIII and IX deficiency. Transplantation in this situation corrects not only the acquired liver disease but the inborn error of metabolism17

Inherited metabolic disorders leading to extrahepatic disease

These inherited diseases include Crigler-Najjar type I, primary oxalosis, familial hypercholesterolaemia, the urea cycle defects, and propionic acidemia.
In Crigler-Najjar type I, the urea cycle defects, and propionic acidemia, medical treatment may not provide adequate metabolic control. There is a constant risk of acute metabolic deterioration leading to a reduction in quality of life and an uncertain future with regard to mental development. Liver transplantation is indicated in those children with recurrent problems whose quality of life is unacceptable. The timing of the operation is important and should be performed before there is irreversible mental deterioration.

Successful liver transplantation has been shown to correct the metabolic abnormalities in a number of urea cycle defects,18 propionic acidemia (personal observation), and to achieve normal bilirubin conjugation in children with Crigler-Najjar type I disease.19

In primary oxalosis the situation is more complex, as the deficiency of the hepatic enzyme alanine-glyoxylate-amino transferase leads to renal failure and bone disease secondary to oxalate deposits. Successful management of this condition requires liver transplantation before the development of renal failure.20 If renal failure is advanced a combined liver and kidney transplant is mandatory.20

Although plasmapheresis or medical treatment may control cholesterol concentrations in heterozygotes with familial hypercholesterolaemia it is unlikely that this therapy will prevent the development of coronary artery disease in homozygote patients. As the metabolic defect is associated with a relative deficiency of low density lipoprotein receptors on hepatocytes, liver transplantation successfully corrects the abnormal cholesterol metabolism.21 Transplantation before development of coronary artery disease is most appropriate but successful liver/heart transplantation has been achieved.21

Transplantation for Niemann-Pick disease (type A, B, or C) is universally unsuccessful,22 while the combination of bone marrow and liver transplantation for this condition remains an experimental option.

**Patient selection and timing of transplantation**

The selection of patients and the timing of transplantation are crucial.

The quality of the patient's life and the long term prognosis of the disease must be balanced against the risks and complications of liver transplantation. In all cases liver transplantation should be performed before there is irreversible extrahepatic disease. In general it is easier to find an age and size matched donor when the child is older and thus the timing of transplantation should take this into account.

In those disorders in which the hepatic enzyme deficiency leads to liver destruction, patient selection and timing depends on the rate of progression of the liver disease, the number of hepatic complications, and the quality of life achieved by the child.

Counselling and education of parents and children is essential, particularly for those children with extrahepatic disease, as the parents must fully understand the implications of liver transplantation, which may be a life threatening procedure, in the context of their child's illness and prognosis.

**The operative procedure**

Liver grafts are selected on the basis of ABO compatibility and size and, if possible, by cytomegalovirus status. The shortage of paediatric donors has been much alleviated by the successful development of reduction hepatectomy which extends the age and size range of transplantation to very young babies with comparable results to whole graft transplantation.23

In children with hepatic disease and portal hypertension, orthotopic replacement of the liver (OLT) is the most appropriate option. However, in children with morphologically normal livers, OLT has a number of disadvantages, the most significant being death from graft failure. It is for this reason that auxiliary heterotopic liver transplantation, in which the segmental liver graft is placed close to the native liver, has been considered. Initially, significant problems with vascular supply and lack of space within the peritoneal cavity lead to poor clinical results and failure of acceptance of this technique.

More recently, technical advances have encouraged the development of orthotopic auxiliary liver transplantation in which the left lateral segments of the patient's liver are replaced with the same segments from a donor liver.24 Recent reports of successful auxiliary liver transplantation for Crigler-Najjar type I disease despite the development of both acute and chronic rejection in the auxiliary liver, are encouraging.25

Although this form of transplantation would seem most appropriate for those disorders in which the liver is normal (Crigler-Najjar type I, urea cycle defects, familial hypercholesterolaemia) it may not be appropriate treatment for all metabolic disorders.

In primary oxalosis where the metabolic defect is the over production of oxalate, there would not be sufficient enzyme in the small transplanted segment to reduce the excess production of oxalate in the native liver.

Likewise, it is not yet clear whether adequate liver tissue would be available from segmental auxiliary transplant to correct the enzyme defects in urea cycle defects or replace the abnormal low density lipoprotein receptors in familial hypercholesterolaemia.

Further experience is clearly required to evaluate how effective this technique is in a wide range of inborn errors of metabolism.

**After the transplant**

**IMMUNOSUPPRESSION**

Most centres prevent graft rejection with triple immuno-suppression with prednisolone, azathioprine, and cyclosporin and reduce the number of drugs and dosage with time. There is still a requirement for lifelong immuno-suppression with cyclosporin with the inevitable side effects of hirsutism and nephrotoxicity. Nephrotoxicity may be particularly troublesome for children with impaired renal function secondary to renal tubular acidosis before transplant.4

**CORRECTION OF THE METABOLIC DEFECT**

In α1-antitrypsin deficiency, Byler's disease, Wilson's disease, and neonatal haemochromatosis there is both phenotypic and functional cure. In tyrosinaemia type I, liver transplantation corrects the hepatic enzyme deficiency and cures the liver failure and is effective prophylaxis for hepatic cancer, although the kidney continues to produce toxic metabolites.

In Crigler-Najjar type I, and the urea cycle defects, the metabolic defect is completely corrected. In primary oxalosis although the metabolic defect is corrected, the postoperative course is determined by the extent of preoperative oxalate deposition and renal function particularly after a combined liver/kidney transplant.

**POSTOPERATIVE COMPLICATIONS**

Liver transplantation remains a high risk procedure with a mortality of 10–20% with high perioperative morbidity.
Children transplanted for inborn errors of metabolism experience the same surgical and medical complications as children transplanted for liver failure. The commonest complications are rejection (60%), sepsis (70%), and technical problems – arterial and venous thrombosis (20%) and biliary complications (20%) with biliary leaks and/or strictures.

SURVIVAL AND QUALITY OF LIFE
One year survival for liver transplantation in children transplanted for liver failure ranges from 80–85% with 75% surviving for five years. A number of studies suggest that children transplanted for inherited metabolic disease have a less difficult course after transplant with improved survival. One year survival rates of 95% have been reported with a four year survival rate of 88%.1

Long term problems are related to immunosuppression, nephrotoxicity, an increase in viral infection with cytomegalovirus and Epstein-Barr virus,23 and the potential development of lymphoproliferative disease.

Survivors have a dramatic improvement in quality of life as the strict dietary regimens and complex metabolic control become redundant. Thus many of these children will be restored to a normal, albeit medically monitored, life.

Summary
Liver transplantation for inherited metabolic disease is a therapeutic reality in the 1990s. Careful patient selection and timing and choice of operative procedure should greatly improve the quality of life and long term survival for those children with life threatening metabolic disease. The rapid expansion of molecular genetics and the development of effective gene therapy may well displace liver transplantation as appropriate treatment of these disorders in the future.

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