Liver transplantation for inherited metabolic disease

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Abstract

Liver Transplantation is indicated for children with inherited metabolic disease because of a primary hepatic enzyme deficiency, which leads to liver failure and/or hepatic cancer, or severe extra hepatic disease. The selection and timing depends on the rate of progression of disease, the success of medical therapy and the extent of reversible extra hepatic disease. Transplant techniques include orthotopic, living related and auxiliary liver transplantation or combined liver and kidney transplantation.

Liver transplantation effectively treats structural metabolic hepatic disease with a phenonotypic and functional cure in alpha1 antitrypsin deficiency, Wilson's disease, PFIC and neonatal haemochromatosis. There is only a partial cure in Tyrosinaemia Type 1 as abnormal metabolites are still produced by the kidney, but a complete cure in primary oxalosis and urea cycle defects. Outcome for organic acidaemias remains poor due to technical and metabolic challenges.

The advent of successful immunosuppression and improved survival rates for liver transplantation has extended the indications to the treatment of inherited metabolic disease.

The aim of liver transplantation in this situation is to cure the inherited metabolic defect both functionally and phenotypically. It is indicated in children with inborn errors of metabolism due to primary hepatic enzyme deficiency which either leads to liver disease and hepatic cancer or to severe extra hepatic disease. In some cases liver transplantation may be required in combination with kidney, heart or bone marrow transplantation.

Inherited metabolic disorders leading to hepatic disease

1. Specific hepatic enzyme deficiencies leading to acute or chronic liver failure and/or development of hepatic cancer : - alpha-1-antitrypsin deficiency, tyrosinaemia type 1, glycogen storage disease type 4.
2. Liver failure secondary to unknown hepatic enzyme defect :- Wilson's disease, Byler's disease, neonatal haemochromatosis.
3. Hepatic enzyme deficiency leading to acquired liver disease. Factor VIII and IX deficiency with subsequent viral hepatitis.

Inherited metabolic disorders, leading to extra hepatic disease

Crigler-Najjar Type I, primary oxalosis, familial hypercholesterolaemia, urea cycle defects and organic academia.

Patient selection and timing of transplantation

The selection of patients and timing of transplantation depends on the enzyme deficiency, the extent of hepatic or extra hepatic disease, the quality of life and outcome and the availability of medical treatment.

Contra-indications for liver transplantation for metabolic disease

The current contra-indications include those children with severe extra hepatic disease which will not reverse post transplantation (eg. severe systemic oxalosis, mitochondrial disorders with associated muscle and neurological degeneration).

Operative techniques

The successful development of reduction hepatectomy, split liver transplantation and living related transplantation has extended the age and size range of transplantation to young babies with comparable results to whole graft transplantation.

As many children with metabolic disease have morphologically normal livers, auxiliary liver transplantation is an option. In this technique the left lateral segments of the patient's liver are replaced with the same segments from a donor liver. Despite initial technical difficulties this technique has proved successful for patients with Crigler Najjar Type I and mild propionic acidemia. Living related liver transplantation is also effective in certain disorders.

Post-operative management

The post operative management of children with inherited metabolic disease is similar to other indications. Most centres prevent graft rejection with either Prednisolone, Azathioprine, Cyclosporin or Tacrolimus and reduce the number of drugs and dosage with time. The range of surgical and medical complications is similar for those children transplanted for liver failure. The commonest complications are rejection 50%, sepsis

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75%, arterial and venous thrombosis 10-20% and biliary complications 10-20%.

Correction of the metabolic defect

In alpha-1-antitrypsin deficiency, Byler's disease and Wilson's disease there will be both phenotypic and functional cure. In tyrosinaemia type 1 liver transplantation corrects the hepatic enzyme deficiency and prevents the development of liver cancer although the kidney continues to produce toxic metabolites. In Crigley-Najjar Type I, urea cycle defects and primary oxalosis, the metabolic defect is completely corrected. In the organic acidemias the metabolic defect is widespread throughout body tissue but liver replacement provides sufficient hepatic enzyme to prevent metabolic acidosis under normal conditions. However, these children are still at risk of mild metabolic acidosis during intercurrent infections and outcome overall remains poor.

Survival and quality of life

One year survival for liver transplantation in children ranges from 90-95% with 80% surviving 5 years. A number of studies suggest that children transplanted for inherited metabolic disease have improved survival with one year survival rates of 95% and 4 year survival rates of 88%.

Long term problems are related to immunosuppression, nephrotoxicity, an increase in viral infections and the potential to develop lymphoproliferative disease. Nevertheless, survivors have dramatic improvement in quality of life as their strict dietary regimes and difficult metabolic control become redundant.

The future development of molecular genetics, effective gene therapy and hepatocyte or stem cell therapy may displace liver transplantation as treatment of these disorders in the future.

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