Medical progress and pitfalls of the treatment of inborn errors involving the liver

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In the early years because of the high risk of mortality and morbidity, liver transplantation was only used for those that were terminally ill. As the outlook for liver transplantation in childhood has improved so the indications for transplantation for metabolic disorders in childhood have expanded (1).

Liver transplantation is used to treat inborn errors for two major indications; firstly because of irreversible liver disease, usually cirrhosis, and secondly for enzyme replacement. The management may be made more complicated by the involvement of other organs by the metabolic disease.

The indications for transplantation for isolated liver failure are the same as those for any other cause. The most frequent disorders are progressive familial intrahepatic cholestasis (PFIC), Wilson's disease, α1- antitrypsin deficiency and tyrosinaemia type 1. In glycogen storage disease (GSD) IV, cystic fibrosis, respiratory chain disorders, and cholesterol ester storage disease liver may be also diseased but other organs are often involved (heart, lung, etc) and may complicate transplantation.

Liver transplantation for enzyme replacement has been done for many disorders. These include Crigler-Najjar, hyperoxaluria, GSD type 1, maple syrup urine disease and urea cycle disorders (most often carbamyl phosphate synthetase and ornithine transcarbamylase deficiencies). The disorder frequently involves other organs, for example in methylmalonic acidaemia, respiratory chain disorders and hyperoxaluria. For this reason in hyperoxaluria and methylmalonic acidaemia the liver transplantation is often combined with renal transplantation because of end stage renal failure (2). Early transplantation may be valuable in some disorders to prevent inevitable complications (for example – homozygous familial hypercholesterolaemia) but the indications for many disorders are not clearly defined. These may include poor prognosis despite optimal therapy, risk of additional complications, difficulties with treatment resulting in unstable metabolic control and poor quality of life.

Whilst intellectual function may improve with liver transplantation (3) liver transplantation is generally not indicated in those disorders in which there is already severe systemic complications (systemic oxalosis), severe neurological damage or in which such complications are inevitable such as Alpers disease (4) and Niemann- Pick type C. However the underlying diagnosis may not be apparent when the patients first present, particularly if they present with acute liver failure. However with advances in molecular genetics it may become possible to screen for some disorders, such as Alpers syndrome.

When considering liver transplantation for systemic disorders it is important to understand the condition fully as serious unexpected complications may develop. In methylmalonic acidaemia it was widely thought that liver transplantation would effectively cure the disorder by reducing circulating metabolite concentrations. However it is now recognised that these patients are at risk of neurological complications, particularly around the time of operation but even many years after transplantation (5).

With increasing use of living related donors from a close family relative, the problem of suitability of carriers of metabolic disorders arises. Whilst there does not appear to be a problem with heterozygotes of recessive disorders, female carriers of X-linked conditions, such as ornithine transcarbamylase deficiency, will need very careful assessment.

The enzyme activity necessary to correct the metabolic abnormalities in some disorders is small so that the disorder may be treated effectively by the replacement of only some liver tissue (for example Crigler-Najjar). In which case hepatocyte transplantation or partial auxiliary liver concentration may be all that is necessary but in both these disorders monitoring the viability of the donor tissue is difficult. Partial auxiliary liver transplantation is technically difficult (6) and relatively few patients have had this procedure worldwide. Hepatocyte transplant may be used to bridge a gap before liver transplantation (7).

Liver transplantation for inborn errors is now an established procedure. Whilst the indications for liver failure are clearly defined the timing and indications for the treatment of inborn errors for enzyme replacement therapy are much less so. The outcome of all patients being considered for transplantation needs to be documented carefully so that guidelines can be developed.

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