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Orthotopic liver transplantation for hepatic-based metabolic disorders

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Abstract Between January 1989 and June 1993, a total of 470 liver transplantations were performed at King's College Hospital. Thirty-seven transplantations were performed in 34 patients with liver-based metabolic disease. There were 16 females and 18 males with a median age of 19 years (range 1 month to 62 years). There were 14 patients under 16 years of age. The indications for liver transplantation were Wilson's disease (n = 16), alpha 1-antitrypsin deficiency (n = 10), tyrosinaemia (n = 2), primary hyperoxaluria type 1 (PH1; n = 2), congenital haemochromatosis (n = 1), familial amyloidotic polyneuropathy (FAP; n = 1, familial hypercholesterolaemia) (n = 1) and Crigler-Najjar syndrome type I (CNS1; n = 1). These included two patients who received combined heart-liver grafts for familial hypercholesterolaemia and FAP, respectively. Two patients received combined liver-kidney transplants for PH1. There were four deaths: from sepsis (n = 2), acute hepatic vein obstruction in a left lateral segment graft (n = 1) and portal vein thrombosis with liver necrosis (n = 1). Three patients were retransplanted, one for chronic rejection and two for hepatic artery thrombosis, giving an overall graft survival of 81 % and patient survival of 88 % (30/34), at a mean follow-up of 34 months (range 10–64 months).

Key words Metabolic disorders, liver transplantation · Liver transplantation, metabolic disorders Wilson's disease, liver transplantation

Introduction

Liver transplantation is accepted therapy for a variety of inborn errors of metabolism (IEM), usually characterised by a deficiency of one or more enzyme systems [11]. The special attraction in liver transplantation for this group of diseases is that transplantation not only replaces a structurally damaged organ but also serves as a source of the missing enzyme or protein and, thereby, corrects the underlying metabolic disease. In contrast to other liver diseases, there is no risk of disease recurrence after liver transplantation. The experience of liver transplantation for liver-based IEM at our centre has been reviewed. This experience has led to be the development of liver grafting techniques such as auxiliary transplantation, which may become the treatment of choice for selected non-cirrhotic patients.

Patients and methods

All patients who underwent liver transplantation for liver-based IEM were reviewed. Information was obtained from patient notes and a prospectively entered, computerised surgical data base. This data base (Reflex, Borland) allowed rapid collation of results and

Table 1 Metabolic disorders treated by liver transplantation

Metabolic disorders presenting with chronic liver disease						
Patient no.	Age	Sex	Diagnosis	Graft type	Alive	Follow-up in months
1	24	f	Wilson's disease	Whole liver	no	8
2	8	f	Alpha 1 antitrypsin deficiency	Whole liver	yes	53
3	42	m	Alpha 1 antitrypsin deficiency/ alcoholic liver disease	Whole liver	yes	48
4	51	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	46
5	63	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	45
6	52	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	45
7	7	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	44
8	33	f	Wilson's disease	Whole liver	yes	44
9	22	m	Wilson's disease	Whole liver	yes	40
10	5	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	37
11	3	f	Tyrosinaemia	Segments II III IV	yes	36
12	3	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	20
13	19	m	Alpha 1 antitrypsin deficiency	Whole liver	yes	19
14	22	f	Alpha 1 antitrypsin deficiency	Whole liver	yes	10
15	34	f	Wilson's disease	Whole liver	yes	12
Metabolic disorders presenting with acute liver failure						
Patient no.	Age	Sex	Diagnosis	Graft type	Alive	Follow-up in months
16	31	f	Wilson's disease	Whole liver	yes	64
17	11	m	Wilson's disease	Whole liver	yes	60
18	16	f	Wilson's disease	Whole liver	yes	51
19	14	m	Wilson's disease	Whole liver	yes	49
20	19	f	Wilson's disease	Whole liver	yes	38
21	15	f	Wilson's disease	Whole liver	no	
22	27	m	Wilson's disease	Whole liver	yes	35
23	21	f	Wilson's disease	Whole liver	yes	34
24	0.1	f	Congenital haemochromatosis	Segments II III	no	
25	8	f	Wilson's disease/hepatitis E	Segments II III IV	yes	31
26	17	f	Wilson's disease	Whole liver	yes	26
27	16	m	Wilson's disease	Whole liver	yes	23
28	1	m	Tyrosinaemia	Segments II III	no	
29	19	f	Wilson's disease	Whole liver	yes	13
Non-cirrhotic liver based metabolic disorders						
Patient no.	Age	Sex	Diagnosis	Graft type	Alive	Follow-up in months
30	33	f	Familial hypercholesterolaemia	Liver and heart	yes	44
31	61	m	Familial amyloidosis	Liver and heart	yes	21
32	37	m	Primary hyperoxaluria	Liver and kidney	yes	18
33	32	m	Primary hyperoxaluria	Liver and kidney	yes	16
34	10	m	Crigler-Najjar	Segments II III	yes	14

statistical analysis. Between January 1989 and June 1993, a total of 470 liver transplantations were performed at King's College Hospital. Thirty-seven of these transplantations were performed in 34 patients with liver-based metabolic disorders. There were 16 females and 18 males with a median age of 19 years (range 1 month to 62 years). There were 14 patients under 16 years of age.

There were eight different liver-based metabolic abnormalities transplanted in this series. The most frequent indications were for Wilson's disease ($n = 16$) and alpha 1-antitrypsin deficiency ($n = 10$). Other indications included tyrosinaemia ($n = 2$), primary hyperoxaluria type 1 (PHI; $n = 2$), congenital haemochromatosis ($n = 1$), familial amyloidotic polyneuropathy (FAP; $n = 1$), familial hypercholesterolaemia ($n = 1$) and Crigler-Najjar syndrome type I (CNSI; $n = 1$). In four diseases (in five patients) hepatic structure and function were not impaired by the metabolic disorder and the livers were non-cirrhotic (Table 1). Two patients received combined heart-liver grafts for familial hypercholesterolaemia and FAP and two received combined liver-kidney transplants for PH1.

The five non-cirrhotic patients had normal liver function tests. The remaining 29 patients had end-stage liver disease. Twelve out ot 16 patients with Wilson's disease presented with acute hepatic failure. Metabolic and infectious screens were performed in all patients and Wilson's disease was diagnosed on the basis of Kayser-Fleischer rings, urinary copper excretion and tissue levels of copper, where possible [10].

A standard technique was used for orthotopic liver transplantation and veno-venous bypass was used in all adult patients. Graft utilisation included 31 whole liver grafts and 6 reduced grafts, 2 of which were left lobes (segments II, III, IV); 4 were left lateral segments (segments II, III). Five patients under 10 years of age had reduced grafts. The two patients who underwent combined heart and liver transplantation received the grafts sequentially, the heart followed by the liver. Similarly, the combined liver and kidney trans-

plantations were performed sequentially, the liver followed by the kidney. The auxiliary segmental liver graft (segments II and III) for the patient with CNS1 was placed in an orthotopic position after removing the recipient left lateral segment. Immunosuppression was based on cyclosporin, azathioprine and steroids.

Results

Four patients died: from sepsis ($n = 2$), venous outflow obstruction in a left lateral segment graft ($n = 1$) and portal vein thrombosis with liver necrosis ($n = 1$). Three patients were retransplanted, two for hepatic artery thrombosis and one for chronic rejection. The overall graft survival was 81 % and the patient survival was 88 % at a mean follow-up of 34 months (range 10–64 months).

One patient had bile leak at the time of T-tube removal; this was managed conservatively. Other complications included laparotomy for retroperitoneal bleeding in a patient who underwent combined liver-kidney transplantation. Two patients developed adhesive small bowel obstruction at 2 months and 8 months post-transplant; they were treated surgically. One patient developed nodular regenerative hyperplasia due to azathioprine toxicity and underwent porto-caval shunt for recurrent variceal bleeding 2 years post-transplant. All surviving patients are well with normal liver function tests.

Discussion

The indication for liver transplantation in the majority of liver-based IEM is end-stage liver disease with significant structural and functional impairment. In these patients with underlying cirrhosis, orthotopic liver transplantation is the preferred method of treatment because of the possible risk of malignancy in the cirrhotic remnant of long-term survivors [5]. In IEM without liver damage, the purpose of liver transplantation is to provide the missing protein or enzyme. Auxiliary liver transplantation has a potential role in the management of these patients and would provide the missing or defective protein or enzyme [8, 12]. Examples of non-cirrhotic IEM that may be suitable for auxiliary transplantation include CNS1, urea cycle defects [2], disorders of fatty acid metabolism, familial hypercholesterolaemia and haemophilia. However, it is not clear how much liver replacement is necessary for each condition. In some disorders such as PH1 and FAP, it appears that the whole liver has to be replaced to correct the underlying defect, whilst experimental evidence in Gunn rats [6] has shown that as little as 5 % of functioning liver tissue may be adequate to provide the conjugation function of the missing enzyme glucoronyl transferase. Thus, CNS1 may represent an ideal condition for auxiliary liver transplantation. Complications secondary to the deposition of substrate in other organs, such as in PH1 and familial hypercholesterolaemia, may also result in multiorgan transplantation [3, 14].

We have performed two combined liver and kidney transplantations for PH1, a rare autosomal recessive disorder due to a deficiency of the liver-specific enzyme alanine glyoxylate aminotransferase (AGT). As the main route of oxalate excretion is renal, hyperoxaluria leads to calcium oxalate urinary lithiasis and nephrocalcinosis, leading to renal failure. As the liver provides the majority of the body's requirement for AGT, combined liver and kidney transplantation for the treatment of PH1 has the dual purpose of replacing the destroyed kidneys and correcting the enzyme deficiency [13, 14].

One patient underwent combined heart and liver transplantation for FAP. Replacement of the liver alone corrected the underlying metabolic abnormality, but the patient required the heart transplant because of restrictive cardiomyopathy secondary to amyloid deposition in the heart. FAP is a fatal autosomal dominant disorder resulting in progressive peripheral and autonomic neuropathy with associated neural and visceral deposition of amyloid [9]. The amyloid is derived from the Met-30 variant of the plasma protein transthyretin. Liver transplantation results in prompt replacement of variant transthyretin by the donor wild-type in the plasma and this, in the long-term, results in arresting the neurological deterioration and mobilisation of amyloid deposit from nervous tissue and viscera [4]. The patient remains well with normal liver function with no further deterioration in the neurological disease.

One orthotopic segmental liver replacement was performed for an 11-year-old boy with CNS1. The patient was noted to be jaundiced shortly after birth and was diagnosed as having CNS1 at 6 weeks. The bilirubin level had been maintained at 250–300 μmol/l by 15 h of phototherapy daily. He had developed mild pyramidal tract signs in his legs and was referred for transplantation because of concern about progression of the neurological injury. An auxiliary segmental transplant using a donor left lateral segment was placed in the orthotopic position in the recipient. The prothrombin time and serum aspartate transaminase returned to normal levels (1.0 and < 50 IU/l, respectively) by day 5 and remained normal thereafter. The serum bilirubin level fell from a preoperative value of 240 μmol/l to 68 μmol/l by day 7 before rising on day 8 to 126 μmol/l. The patient required no further phototherapy and the bilirubin remained around 100 μmol/l for the next 4 months.

Auxiliary transplantation for CNS1 has been reported before [15] in a 13-year-old girl transplanted with a left lateral segment from a living related donor. Orthotopic segmental transplantation represents a technical advance in the management of non-cirrhotic IEM and,

possibly, for fulminant hepatic failure [1, 7]. With recent advances in the clinical application of gene transfer therapy for the correction of metabolic disorders, it may be necessary to preserve the native liver for such therapy if it becomes available in the future. The technical aspects of the operation have now been refined, but the problems of the timing of transplantation and postoperative monitoring of graft rejection remain.

The safety and efficacy of liver transplantation for metabolic disorders is well established. Improvements in surgical technique and greater understanding of the nature of metabolic disease should result in a re-appraisal of techniques such as auxiliary grafting that preserve the functioning liver yet replace defective enzyme systems until techniques such as gene therapy become a clinical reality.

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