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Orthotopic liver transplantation for acute hepatic failure in children

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Abstract Thirty children received 35 liver transplants for fulminant or late-onset liver failure between March 1988 and May 1993. Aetiology included non-A non-B hepatitis in 12, Wilson's disease in 8, drug-induced hepatic failure in 6, hepatitis B in 1, hepatitis A in 1, tyrosinaemia in 1 and congenital haemochromatosis in 1. Three patients were retransplanted, one each for hepatic artery thrombosis, non-A non-B graft reinfection, and chronic rejection. Two of these three patients received a third transplant for chronic rejection and hepatic artery thrombosis. One patient in the retransplant group survived. Overall, graft and patient survival at a mean follow-up of 17 months were 49% and 57%, respectively. Mortality was related to vascular complications in three patients (hepatic venous obstruction, portal vein thrombosis and hepatic artery thrombosis). Two patients died of primary sepsis (cerebral aspergillosis and cytomegalovirus (CMV) pneumonitis in association with graft-versus-host disease). Systemic sepsis and multiorgan failure was documented as a cause of death in four children and sepsis in association with chronic rejection in a further three patients. One child died of respiratory failure 4 weeks after transplantation. Mortality in eight children less than 2 years was 75% and this was significantly greater than for older children ($P < 0.003$, Mantel Cox). Earlier referral, even in the absence of a definitive diagnosis and particularly in children under 2 years is advisable and may improve survival.

Introduction

Fulminant or late-onset liver failure in children is a rare but life-threatening condition with a mortality that remains between 50 and 90%. Characterized by widespread hepatocyte necrosis, older children present with jaundice, encephalopathy and coagulopathy developing over a period of less than 8 weeks (fulminant) or over a longer period (late-onset). In infants with severe coagulopathy (International Normalized Ratio; INR > 4) the mortality is high even in the absence of encephalopathy. Underlying causes of fulminant hepatic failure include viral infection, drug overdose, idiosyncratic drug reactions and inborn errors of metabolism. The signs of liver impairment may present early and the progression to encephalopathy and death may be rapid [1].

Liver transplantation for fulminant or late-onset hepatic failure has improved the outcome in carefully selected adult patients. Experience of liver transplantation for fulminant hepatic failure in children, especially

those aged less than 2 years, is limited [1–4]. Consequently, the indications and outcome of liver transplantation in these patients are not clearly defined. We have previously reported 66% survival for 12 children transplanted for acute liver failure and now report our experience in a further 18 children [5].

Patients and methods

All patients less than 16 years of age at the time of presentation, who underwent liver transplantation for acute liver failure were reviewed. Information was obtained from patient notes and a prospectively entered, computerized surgical data base. This database (Reflex, Borland) allowed rapid collation of results and statistical analysis. Survival analysis was by the Kaplan Meir method. Life table analysis and the log rank Wilcoxon test were performed to determine levels of significance between survivors in different age groups. An unpaired Student's *t*-test was used to annualize differences between group means with levels of significance taken at the 95% confidence interval.

Liver transplantation was performed for fulminant failure if three or more of the King's College criteria were met [3]. These included age less than 10 years or greater than 40 years, aetiology (drug induced, non-A non-B and halothane hepatitis), jaundice for more than 7 days prior to the onset of encephalopathy, prolongation of prothrombin time greater than 50 s and a serum bilirubin level greater than 300 μmol/l. This unit has previously shown a mortality in adults of 95% without liver transplantation if three or more of these criteria are present [3]. Although there are no established criteria for the timing of transplantation in late-onset hepatic failure, the decision was taken in the presence of severe impairment of liver function, worsening jaundice or encephalopathy. More recently, paediatric patients have been listed for transplantation on the basis of a persistently elevated INR (> 4) and abnormal liver function tests in addition to the grade or progression of encephalopathy. This reflects concern over the rapid development of encephalopathy in children, the difficulties in grading encephalopathy in very young children, and the risk of brain injury and the poor outcome when encephalopathy is a major criterion for transplant listing [2].

Immunoassay techniques were used to test for IgM antibody against hepatitis A, hepatitis B (HBsAg) and hepatitis C viruses. All patients received full supportive care and were managed in an intensive care environment. On admission, grade 1 encephalopathy was noted in six, grade 2 in four, grade 3 in ten and grade 4 in ten patients. Intracranial pressure (ICE) was measured using a Camino bulb (Camino Laboratories, San Diego, California) after correction with fresh-frozen plasma (FFP) and/or plasmapheresis in 11 patients. The range of ICP was 14–45 mm Hg in the survivors and 15–55 mm Hg in the non-survivors ($P > 0.05$). Muscle paralysis with controlled ventilation and intravenous mannitol were used to control cerebral oedema. Coagulation disorders were corrected with FFP, cryoprecipitate and/or exchange transfusion after the decision to transplant had been made. 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 serum and tissue levels of copper where possible [6].

All patients had hyperbilirubinaemia (mean serum bilirubin, 411; range 31–1121 μmol/l) and a mean serum aspartate aminotransferase of 884 IU/l (range 54–6,970). Coagulopathy was present in all patients with a mean INR of 4.3 (range 3.5–12.2). Although coagulopathy was corrected pre-operatively and during transplantation the mean blood loss was 3.7 l (range 1–17.5 l and a mean of 107 ml/kg body weight).

Results

Between February 1988 and February 1993, a total of 483 liver transplants were performed in 431 patients at King's College Hospital. Eighty-six liver transplants were performed in 67 children. Of these, 35 transplants were performed in 30 children for fulminant hepatic failure. There were 17 females and 13 males with a mean age of 9.1 years (range 1 month–17 years) and a mean weight of 33.5 kg (range 3.2–70 kg) at transplantation. The cause of acute hepatic failure was non-A non-B hepatitis in 12 patients, Wilson's disease in 8, drug-induced in 6 (paracetamol in 2, carbamazepine in 3, rifampicin in one), hepatitis A in one, hepatitis B in one, tyrosinaemia in one and congenital haemochromatosis in one.

The mean duration on the urgent waiting list was 4.7 days (range 0–37 days; median, 6.9 days). The mean time on the waiting list for survivors and non-survivors was 3.9 and 5.9 days, respectively, $P > 0.05$. Patients less than 2 years old who survived orthotopic liver transplantation (OLT) spent a mean of 5 days on the waiting list compared to a mean of 7.8 days ($P > 0.05$) for non-survivors. There was no difference in waiting list duration between this group and children aged more than 2 years. Three patients were retransplanted, one each for hepatic artery thrombosis, non-A non-B graft reinfection and chronic rejection. Two patients in this group received a third graft, one each for chronic rejection and hepatic artery thrombosis. Only one patient in the retransplanted group survived. Graft utilization included 17 (49%) whole liver grafts and 18 (51%) reduced grafts, of which 10 were left lobes (segments 2, 3, 4) and 8 were left lateral segments (segments 2, 3).

The choice of graft depended on the relationship of donor and recipient size (mean donor weight, 57.7 kg; range 8.5–88 kg). Biliary reconstruction was by duct-to-duct anastomosis in 19 transplants (internal stent in 2, T-tube in 15, duct-to-duct with no stent in 2), and a Roux-en-Y choledochoenterostomy in 16. An infra-renal iliac artery conduit was used for arterial revascularization in 16 (46%) patients and the remainder underwent direct anastomosis of donor common hepatic artery to recipient common hepatic or coeliac artery.

Seventeen patients were alive and well at a mean of 28 months post transplant (range 3–61 months), giving an overall patient survival of 57%. Thirteen patients died 1 week–14 months after transplantation (mean 2.8

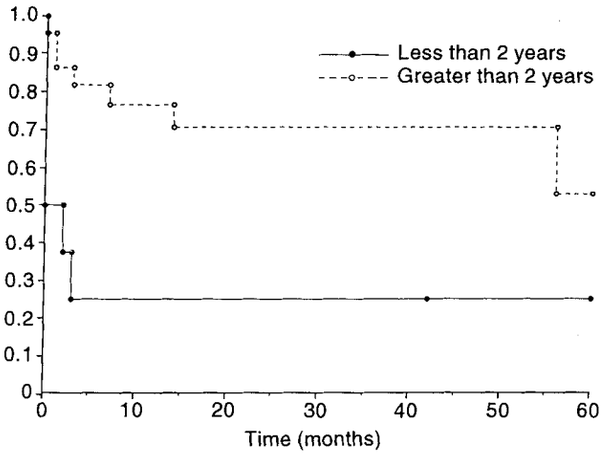

Fig. 1 Patient survival after orthotopic liver transplantation based on Kaplan Meier method. Log rank statistics used to determine levels of significance between outcome in patients less than 2 years compared with older patients ($P < 0.003$) by Mantel Cox. Mortality greatest in first 3 months following transplant

months; see Fig. 1). Survival was not significantly related to severity of INR derangement or grade of encephalopathy. However, the mortality in eight patients aged less than 2 years was 75% (Fig. 1) and was significantly greater than that in older children ($P < 0.003$, Mantel Cox Test).

Overall, graft survival was 49%. Three patients died from vascular complications that included hepatic venous obstruction, portal vein thrombosis and hepatic artery thrombosis (a second patient with hepatic artery thrombosis underwent successful retransplantation). Two patients died of primary sepsis (cerebral aspergillus infection in one patient and CMV pneumonitis and graft-versus-host disease in the other). Sepsis in association with chronic rejection was a cause of death in three patients (2 occurring after retransplantation). Systemic sepsis and multiorgan failure was documented as the cause of death in a further four children. One child died of respiratory failure 4 weeks after transplantation.

Other complications included a bile leak from the cut surface of a reduced graft and perforation of a Roux loop. Both children underwent surgical correction. One patient underwent laparotomy for bleeding from the raw surface of a reduced graft as a result of graft rotation that was corrected by graft fixation. Infective complications included a wound infection managed with dressings and a subphrenic abscess treated by percutaneous drainage.

Discussion

Acute liver failure in young children continues to be associated with a poor outcome. Prognosis has been reported to be dependent on the degree of encephalopathy, aetiology of liver failure, duration on the transplant waiting list and age at presentation [1–3, 7, 8]. The decision to transplant children with acute liver failure is usually based on adult criteria and may not be directly relevant to these patients. Using these criteria, the mortality in adults with three or more prognostic factors exceeds 90% in the absence of OLT [3]. Previous studies have shown that up to 20% of children with acute liver failure may recover spontaneously in the absence of transplantation [1, 8]. The relative rarity of acute paediatric liver failure and the variation in listing criteria between centres makes it necessary to establish specific criteria for children.

In relation to aetiology, non-A non-B hepatitis is less likely to recover spontaneously and more likely to come to transplantation. Severity of encephalopathy has been reported as a significant indicator of poor outcome [1, 2]. However, no correlation was observed in this study. Seven of 17 patients with an encephalopathy grade greater than 2 and 6 of 13 patients with an encephalopathy of grade 2 or less died. This experience contrasts with that of Devictor et al. who have reported no mortality in patients with an encephalopathy grade of less than 2 [1]. This difference may be explained by the difficulties in determining grades of encephalopathy in very small children and also by the relatively long period on the transplant waiting list (mean 4.7 days, range 0–37). Encephalopathy may progress rapidly in young children and these patients should be transferred urgently to a centre with paediatric transplant experience without waiting for a specific diagnosis other than fulminant hepatic failure.

Aggressive management of neurological complications while awaiting transplantation is essential to prevent irreversible brain damage. Cerebral oedema remains a major cause of death in 50% of patients with acute liver failure and every effort should be made to recognize and treat raised ICP [1, 9]. Clinical suspicion based on pupillary changes, bradycardia, hypertension and focal neurological signs warrant endotracheal intubation, controlled ventilation and direct measurement of ICP to ensure adequate cerebral perfusion and oxygenation [9]. Insertion of an ICP probe may present problems with a coexisting coagulopathy, but plasmapheresis and transfusion of fresh-frozen plasma provides a safe window for probe insertion.

Previous reports have suggested that the level of INR derangement of all patients with acute liver failure has prognostic significance [2, 3]. Severity of coagulopathy in this selected group did not correlate with survival after surgery. Reflecting the poor prognosis of this group in the absence of transplantation, survival was not related to other biochemical abnormalities, such as creatinine, bilirubin or aspartate transaminase levels. However, children under 2 years of age with fulminant liver failure had a poorer outcome than older children in this series ($P < 0.003$) and this was particularly pronounced in the first 3 months after surgery (Fig. 1). Technical problems related to small size contributed to death in three of six patients less than 2 years, but were not a factor in older patients.

This group has previously reported a 66% survival following OLT for acute liver failure in 12 children. The overall survival reported in this larger series fell to 57%. This may reflect the difficulty in obtaining appropriate size-matched grafts and the length of time awaiting a suitable organ, but more probably reflects the increase numbers of patients less than 2 years old. Although no information was available concerning the interval between onset of hepatic failure and referral to a transplant centre, it is possible that time spent trying to establish a diagnosis delayed referral. Children with hepatic failure should be referred to a transplant centre without waiting to establish a specific diagnosis, even if there is no evidence of encephalopathy, to allow transplant assessment to occur in tandem with ongoing investigations.

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