Liver transplantation for cirrhosis in cystic fibrosis

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BACKGROUND: Liver disease is the third most common cause of death in children with cystic fibrosis (CF). Liver transplantation is an effective treatment in children with hepatic failure.
AIMS: The objective of the present study was to review the indications and postoperative course of hepatic transplantation in a cystic fibrosis population.
PATIENTS: Five children with CF, at a mean age of 16.5 years, underwent liver transplantation.
RESULTS: All patients showed cirrhosis, portal hypertension and hepatic failure. The main postoperative complication was ascites refractory to treatment in two patients. No significant deterioration of the pulmonary function was noted. Two patients died, one of Hodgkin lymphoma and the other of progressive pulmonary failure.
CONCLUSION: Liver transplantation was indicated in children with CF when hepatic failure and/or severe portal hypertension was present with well-preserved pulmonary function.

Key Words: *Cirrhosis; Cystic fibrosis; Hepatic failure; Liver transplantation; Portal hypertension*

Transplantation hépatique et cirrhose du foie dans le contexte de la mucoviscidose

CONTEXTE : Les lésions hépatiques constituent la troisième cause de mortalité chez les enfants atteints de mucoviscidose. La greffe du foie s'avère un traitement efficace chez les enfants souffrant d'insuffisance hépatique.
BUT : L'étude avait pour but de passer en revue les indications de la transplantation hépatique et son évolution postopératoire chez des patients atteints de mucoviscidose.
PATIENTS : Cinq enfants atteints de mucoviscidose (âge moyen : 16,5 ans) ont subi une transplantation hépatique.
RÉSULTATS : Tous les patients souffraient de cirrhose, d'hypertension portale et d'insuffisance hépatique. La principale complication postopératoire a été l'ascite réfractaire au traitement chez deux patients. Aucune détérioration fonctionnelle importante des poumons n'a été observée. Deux patients sont morts : l'un de la maladie de Hodgkin; l'autre, d'insuffisance pulmonaire évolutive.
CONCLUSION : La transplantation hépatique est indiquée chez les enfants atteints de mucoviscidose, qui souffrent d'insuffisance hépatique ou d'hypertension portale grave, mais chez qui le fonctionnement respiratoire est toujours bon.

The development of biliary cirrhosis in patients with cystic fibrosis (CF) is attributed to obstruction of intrahepatic bile ductules by abnormal mucoid secretions or inspissated bile, resulting from the absence of CF transmembrane conductance regulators in biliary epithelial cells (1). While advances in pulmonary management and anti-infectious therapy have improved life expectancy in CF, patients are being followed more frequently for extrapulmonary complications. Liver disease usually presents in childhood and is now more commonly recognized at an earlier age (2). As the survival rates of CF patients improve, advanced liver disease is becoming more prevalent and is now considered to be the third most common cause of death in these patients (3-5). Once portal hypertension is established, the prognosis is poor: 20% of affected children die as a direct result of the liver disease, with a mean survival of only 4.5 years (6). An excess of respiratory deaths has been noted in children with liver disease (4,6). As a result, portosystemic shunting has been proposed to control complications of portal hypertension while liver function is still preserved (6). However, liver transplantation (LT) offers a potentially curative treatment for end-stage liver disease in these patients. Combined lung and liver transplantation has been performed, but the outcome has not been satisfactory (7). In patients with preserved pulmonary function, isolated LT may be proposed (8-12). However, some physicians may be reluctant to refer patients for evaluation due to concerns over pre-existing pulmonary disease and its potential progression under immunosuppression following transplantation.

We report the indications and postoperative course in five children with CF and hepatic cirrhosis requiring liver transplantation between 1992 and 2001.

PATIENTS

Of the 241 CF patients followed by the Cystic Fibrosis Clinic of Sainte-Justine Hospital (Montreal, Quebec) between 1992 and 2001, five (four male and one female) patients required liver transplantation for advanced hepatic cirrhosis (Table 1). The diagnosis of CF was made at a median age of two months (range one to 12 months) and they presented with meconium ileus requiring intestinal resection (two patients), chronic cough (one patient) or growth retardation (one patient). One patient was diagnosed through family screening. Patients were followed up for a median period of 17.5 years (range 16.5 to 20.5 years). All patients were pancreatic-insufficient and had been treated with pancreatic enzymes since the age of three months (range one to 60 months). Liver disease was first detected at a median age of six years (range four to 13 years), with elevated aminotransferases or gamma-glutamyl transferases found in all patients, hepatomegaly in

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TABLE 1
Characteristics of cystic fibrosis (CF) patients undergoing liver transplantation (LT)

Patient characteristics	1	2	3	4	5
Sex	M	M	M	M	F
Age at diagnosis of CF (months)	2	7	12	1	1
Age at diagnosis of liver disease (years)	6	13	4	5	8
Age at diagnosis of cirrhosis (years)	7.5	13	9	10	10.5
Age at transplantation (years)	13	17.5	13	18.5	16.5
Before transplantation					
Platelets ($\times 10^9$/L)	58	45	84	94	37
International normalized ratio	1.8	2.2	1.29	1.26	1.98
Factor V (%)	28	28	37	45	25
Albumin (g/L)	32	34	31	39	36
White blood cell ($\times 10^9$/L)	3300	1200	3200	4100	4200
Indication for LT	HF	HF	HF	HF	HF
	–	–	PHT	PHT	PHT

F Female; HF Hepatic failure; M Male; PHT Portal hypertension

TABLE 2
Outcome in cystic fibrosis patients undergoing liver transplantation (LT)

Outcomes	1	2	3	4	5
BMI (kg/m^2) (percentile)					
Pre-LT	19 (75)	23 (80)	13.7 (<3)	19.6 (25)	16.4 (<3)
One year after LT	21.4 (80)	24 (80)	15 (<3)	20 (25)	16.6 (<3)
FVC (%)					
Pre-LT	99	97	80	117	90
One year after LT	102	97	84	117	92
FEV_1 (%)					
Pre-LT	79	90	60	98	78
One year after LT	87	95	65	106	68
Outcome	Alive	Alive	Dead (Hodgkin lymphoma)	Alive	Dead (pulmonary failure)
Follow-up post-LT (year)	9	1.5	8	4	12

BMI Body mass index; FEV_1 Forced expiratory volume in 1 s (% predicted); FVC Forced vital capacity (% predicted)

two patients, or heterogenous liver parenchyma on ultrasound examination in three patients. Diagnosis of cirrhosis was made at a median age of 10 years (range 7.5 to 13 years), with signs of portal hypertension already present in three patients. Four patients received a treatment with ursodeoxycholic acid but in three of them, it was started once cirrhosis was already present. At the time of LT assessment, all five patients had portal hypertension with splenomegaly and hypersplenism (thrombocytopenia). One patient had episodes of rectal bleeding and three had suffered life-threatening upper intestinal bleeding, requiring repeated variceal sclerotherapy or banding procedures. All had hepatic failure with decreased factor V (25% to 45%) and three patients had hypoalbuminemia. All patients had moderate pulmonary disease (forced vital capacity 80% to 117%, forced expiratory volume in 1 s 60% to 98% of predicted value). In our institution, we considered it reasonable to pursue liver transplant in patients with forced expiratory volume in 1 s or forced vital capacities greater than 60%. The upper respiratory tract was colonized with *Pseudomonas aeruginosa* (five patients), *Aspergillus fulmigatus* (four patients), *Staphylococcus aureus* (one patient) and *Stenotrophomonas maltophilia* (one patient). In patient 3, LT occured after a 15-day course of intensive physiotherapy and intravenous (IV) tobramycin before LT. Two patients had evidence of malnutrition, with a body mass index (BMI) of 13.7 kg/m^2 (patient 3) and 16.4 kg/m^2 (patient 5), respectively (Table 2).

RESULTS

LT was indicated in the patients over one to two years because of deterioration in hepatic synthetic function along with associated severe gastrointestinal hemorrhage in patient 3. Orthotopic LT was performed at a median age of 16.5 years (range 13 to 18.5 years) with whole cadaveric donor organs. The median duration of operation was 10 h (7 h to 13.2 h). The biliary anastomosis was choledocojejunal (three patients), choledococholedocal (one patient) or choledocoduodenal (one patient).

The initial immunosuppressive protocol consisted of IV cyclosporin (5 mg/kg/day), azathioprine (2 mg/kg/day) and methylprednisolone (2 mg/kg/day). Patient 5 also received murine monoclonal antibody-OKT3 then antithymocyte globulin until postoperative day 10, because of transient renal insufficiency. Oral medications were introduced between day 6 and day 14, but pharmacokinetic profiles showed variable absorption of oral cyclosporin in two patients. Absorption of cyclosporine improved with the administration of diltiazem in patient 4, while patient 5 (the first patient treated with Neoral [Novartis Pharmaceuticals, Canada]) required prolonged IV administration and, finally, a switch to tacrolimus.

Postoperative complications included acute graft rejection treated by IV bolus of corticosteroids (two patients), delayed liver function attributed to prolonged cold ischemia (one patient), glucose intolerance requiring insulin (two patients) and cholangitis (one patient). IV antibiotics directed against bacteria colonizing the respiratory tract before LT (*P aeruginosa*, *A fulmigatus*, *S aureus*, or *S maltophilia*) were administered in the postoperative days and no infection occurred. Patient 3 presented a fever on postoperative day 20 because of cytomegalovirus infection, confirmed by positive antigenemia. It was succesfully treated with a 15-day course of ganciclovir. This patient, who was negative for Epstein-Barr virus (EBV) serology and received a liver graft from an EBV-positive donor, was treated with acyclovir for 12 days for the presence of EBV-positive monocytes in ascites fluid at postoperative day 90. *Candida albicans* septicemia was successfully treated with fluconazole in patient 4. Patient 3 developed a bile leak that required the reconstruction of the choledocojejunal anastomosis on postoperative day 3. No biliary obstruction was observed subsequently. Patient 2 developed EBV-induced post-transplant proliferative disease in the liver, which was controlled by decreasing the immunosuppressive treatment.

Three patients developed ascites, which in two patients were refractory to treatment for a long period of time (five months and 14 months, respectively). These two patients were malnourished and required repeated abdominal paracentesis. Patient 5 also required prolonged parenteral nutrition. The median duration of stay in the intensive care unit was seven days and the median total duration of hospitalization after LT was one month (range three weeks to nine months).

One year after LT, no significant deterioration of the pulmonary function was noted and BMI improved but remained under the third percentile in the two malnourished patients. Three patients were alive, one-and-a-half, four and nine years after LT. One patient died from Hodgkin lymphoma eight years after LT and another, who developed progressive pulmonary failure, refused lung transplantation and died 12 years after LT.

DISCUSSION

The reported prevalence of clinically apparent liver disease in CF is variable, ranging from 2.2% to 24.5% (4). Although ursodeoxycholic acid improves nutritional status and blood concentrations of liver enzymes (13), there is no direct evidence that this treatment is accompanied by delay or reversal of liver fibrosis or portal hypertension. Hepatic cirrhosis has been reported to occur in 7% of patients (6) and is associated with increased mortality either directly or from deterioration in pulmonary disease. Surgical portosystemic shunting has been considered in patients with severe portal hypertension but without progressive liver failure (14,15). However, the transient benefit of such an intervention has reduced its widespread application and isolated LT has become a therapeutic option for the treatment of end-stage liver disease in patients with well-preserved pulmonary function (8,9,16).

Besides liver function, pre-LT evaluation should also include bacteriological examination of the sputum, pulmonary function, glucose intolerance and nutritional status. The first concern relates to the use of immunosuppressive agents when the lungs are colonized by microbial pathogens. The patient in the first case of LT in CF reported by Cox et al (17) died of a cerebral abscess with *A fulmigatus*, and a high postoperative mortality rate due to infection raised concerns in some series (10,18). An intensive preoperative physiotherapy and systematic postoperative prophylactic antibiotic administration directed against bacteria present in the upper respiratory tract at the time of LT, led to a dramatic decrease of infectious complications despite the use of immunosuppression (11,12,19,20). These authors also showed that respiratory function remained stable or even improved after LT (11,12,19,20) and that the children demonstrated an improved exercise tolerance and a decreased sputum production (11). After LT, resolution of several problems frequently associated with cirrhosis and portal hypertension, such as abdominal distension and diaphragmatic splinting, intrapulmonary shunting, pulmonary edema and malnutrition could explain this unexpected benefit (11). In addition, immunosuppressive therapy may block cytokine production, resulting in the inhibition of pulmonary inflammation (21). In our patients, pulmonary function remained stable or slightly decreased during the year following the LT. Although diabetes has been found to be more frequent in CF patients with severe liver disease (12), none of our patients presented with preoperative diabetes. Nevertheless, two patients needed insulin for glucose intolerance temporarily after the LT, which could have been related to the use of corticosteroids. In contrast, Noble-Jamieson et al (11) reported a child with pretransplant diabetes who enjoyed a prolonged remission after LT.

In two of our patients, a decreased absorption of cyclosporine was observed. Decreased absorption of cyclosporine requiring increasing doses has been reported (11,12) and has been improved with the use of a microemulsion, Neoral (Novartis Pharmaceuticals, Canada) (22), with the administration of vitamin E in a polyethylene glycol-based form or with the administration of agents that inhibit intestinal and liver metabolism of cyclosporine (23). Biliary obstruction has been frequently reported as a potential complication of duct-to-duct biliary anastomosis (24). The only patient in our series to have such an anastomosis did not develop biliary obstruction. One of the original findings of our series was the occurrence of refractory ascites in three patients. Two of the three patients were malnourished and required repeated paracentesis leading to prolonged hospitalization (five and 14 months, respectively). Although uncommon, massive ascites represents a serious complication of LT (25-28), which can occur secondary to thrombosis or stenosis of the portal vein or the hepatic artery, perihepatic lymphatic vessels, chronic graft rejection or hypoproteinemia associated with severe malnutrition and an increased mortality after LT (8,29). Massive ascitic fluid loss can also lead to hypovolemia and major coagulation disturbances favouring thrombosis (30). The risk of ascites and the increased mortality rate (18) in undernourished children underlines the necessity of an early aggressive nutritional management, such as enteral feeding or parenteral nutrition. In case of persistent weight loss or BMI drop under the third percentile, patients should be considered as candidates for LT.

The favourable outcome in the present series of patients confirmed that isolated LT is the procedure of choice in CF patients with hepatic cirrhosis and severe portal hypertension and/or hepatic failure and well-preserved pulmonary function. Postoperative complications such as severe ascites occur mainly in malnourished patients, underlining the importance of aggressive nutritional support and of early listing of these patients before advanced malnutrition takes place.

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