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Original Article

Simultaneous liver–pancreas transplantation for cystic fibrosis-related liver disease: A multicenter experience☆

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Abstract

Background: Diabetes is associated with increased morbidity and mortality in patients with cystic fibrosis (CF). While liver transplantation is well established for CF-related liver disease (CFLD), the role of simultaneous liver–pancreas transplantation is less understood.
Methods: We polled 81 pediatric transplantation centers to identify and characterize subjects who had undergone simultaneous liver–pancreas transplantation and obtain opinions about this procedure in CFLD.
Results: Fifty (61.7%) polled transplant centers responded and 94% reported that they would consider simultaneous liver–pancreas transplantation for CFLD and diabetes. A total of 8 patients with simultaneous liver–pancreas transplantation were identified with median follow up of 38 months. All patients had pre-existing diabetes. Exocrine and endocrine pancreatic function was initially restored in all patients with later functional loss in one patient. Body mass index Z-score increased between one year pre-transplantation and one year post-transplantation ($P = 0.029$).
Conclusions: Patients with CFLD undergoing initial assessment for liver transplantation may benefit from consideration of simultaneous liver–pancreas transplantation.

Keywords: Cystic fibrosis; Simultaneous liver pancreas transplantation; Retrospective; Cohort; Clinical; Diabetes

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive multisystem disorder in which defective epithelial chloride transport across membranes causes dehydrated, thick, viscous secretions. While CF has a highly variable presentation and course, most CF patients are expected to reach adulthood due to advances in medical therapy

☆ These results have been presented in abstract form at The European Association for the Study of the Liver, Barcelona (Spain), April 18–22, 2012 [1].

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[2], and attention to optimizing the outcomes of extra-pulmonary complications such as liver and pancreatic disease is increasing. Cystic fibrosis-related diabetes is a principal non-pulmonary CF complication, with 35–50% of CF patients developing insulin-dependent diabetes mellitus before the age of 30 years [2]. The cumulative incidence of liver disease in CF patients (CFLD) ranges from 27% to 35%, with progression to clinically significant portal hypertension and related complications of cirrhosis affecting approximately 5–10% of all CF patients [3]. The mean age for developing liver disease in CF is prior to puberty in the mid-childhood years [4].

Liver failure and complications of portal hypertension are the common indications for liver transplantation in CF patients. While long-term outcomes in patients with CFLD are acceptable, they are still inferior in comparison with the outcomes of those undergoing liver transplantation for other primary liver conditions [3]. However, progressive lung disease could play an important role in inferior outcome and a clear survival benefit is demonstrated in both adult and pediatric patients following liver transplantation in comparison with those who remained on the waiting list [5].

Distinct from the high prevalence of pancreatic insufficiency and cystic fibrosis related diabetes in CF patients, epidemiological data indicates that CFLD is an independent risk factor for developing cystic fibrosis related diabetes [6]. While all patients have an increased risk of developing diabetes following liver transplantation, the majority of CFLD patients develop diabetes after transplantation [7]. Thus restoration of endocrine and exocrine pancreatic function after simultaneous pancreas transplantation may offer considerable improvement in health and quality of life by alleviating the need for insulin and pancreatic enzyme replacement therapy and could lead to improved growth and nutritional status. In addition, it might decrease the well known long-term complications of CF, such as microvascular disease. To date, simultaneous liver–pancreas transplantation has been reported by four liver transplant centers in the United Kingdom, USA and Spain in a total of seven children with CF [8–11]. Herein, the aims of this study were (a) to identify subjects who had undergone simultaneous liver pancreas transplants including those already reported (b) to evaluate their clinical outcomes, including the longer term outcomes of those already reported (c) and to survey attitudes of transplant physicians concerning the role of simultaneous liver–pancreas transplants in CFLD.

2. Methods

2.1. Survey

Eighty-one pediatric liver transplantation programs within North America, Europe and Oceania were identified from established pediatric liver transplantation registries European Liver Transplant Registry (ELTR; www.eltr.org) and Studies of Pediatric Liver Transplant (SPLIT; www.split.com). Transplant hepatologists and/or liver transplant surgeons (one per site) were approached by email invitation to participate in an online survey (http://nl.surveymonkey.com) on simultaneous liver–pancreas transplantation (Table 1). A follow-up email was sent four weeks later.

Table 1
Online survey on combined liver–pancreas transplantation.

1. If the opportunity presented itself, would your institution consider doing a combined liver–pancreas transplant in a CF patient meeting criteria for liver transplantation?
   A. With CF-related diabetes mellitus
   B. With impaired glucose tolerance
   C. With normal glucose tolerance test but exocrine pancreatic insufficiency
   D. No, under no circumstances
2. If no, please state reason
   A. Increased surgical risk
   B. Increased risk of rejection
   C. Poor outcome at other centers
   D. Lack of experience with combined transplant
   E. Other (please state)
3. What kind of surgical technique would you consider?
   A. Separate liver pancreas
   B. En bloc technique
   C. Both
4. For what ages would you consider doing a liver–pancreas transplant?
   A. Only adults
   B. Above 12 years of age
   C. Above 1 year of age
   D. All ages
5. Do you feel there are contraindications for doing a liver–pancreas transplant in CF patients? If yes please state reason(s).
   A. Yes
   B. No
6. Has your institution performed one or more liver–pancreas transplants in CF patients?
   A. Yes
   B. No

2.2. Study patient population

Transplant centers that had performed simultaneous liver–pancreas transplantation were invited to provide additional clinical information. All patients who developed CFLD before the age of 18 years and who underwent simultaneous liver–pancreas transplantation between 1995 and 2011 were included in our study. Patients receiving a liver–kidney or liver–lung transplants were excluded from the study. Human research ethics approval was obtained from all participating centers that had performed at least one simultaneous liver–pancreas transplant.

2.3. Data gathering and analysis

Data containing general patient information, pancreatic, liver, pulmonary and renal function, and laboratory tests were obtained for all included simultaneous liver–pancreas transplantation recipients and are summarized in Supplementary Table 1. Endocrine pancreas insufficiency was defined as having overt diabetes mellitus requiring chronic insulin therapy. Exocrine pancreas insufficiency was defined by the need for long term pancreatic enzyme replacement therapy. Laboratory investigations included concentration of platelets, alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), bilirubin, albumin and coagulation studies [international