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Survival of childhood polycystic kidney disease following renal transplantation: The impact of advanced hepatobiliary disease

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Abstract: Childhood PKD encompasses the diagnoses of AR and ADPKD, glomerulocystic disease, and syndromes such as tuberous sclerosis or Jeune's syndrome. Given the fact that a majority of PKD children with ESRD carry the diagnosis of ARPKD, natural history studies assessing the long-term prognosis of PKD patients following renal transplantation must focus on morbidity and mortality issues related to complications from congenital hepatic fibrosis. Using the NAPRTCS registry, we analyzed the patient and graft survival rates of 203 PKD patients and 7044 non-PKD patients undergoing renal transplantation between 1987 and 2001. Deceased PKD patients, all with a diagnosis of ARPKD, were further identified and characterized using a special questionnaire submitted to the principal investigators. Overall graft and patient survival rates were not significantly different between PKD and non-PKD patients. No differences in rates of acute rejection or time to first rejection were noted between PKD and non-PKD patients. The relative risk of living longer than 3 yr in the PKD patients was not significantly different from non-PKD patients (RR = 0.70, p = 0.28). Sepsis was identified as a likely factor in the cause of death in nine (64%) ARPKD patients and was comfirmed with a positive blood culture in four patients. Despite similar graft and patient survival rates among PKD and non-PKD children following renal transplantation, our results suggest that ARPKD transplant recipients appear to be at increased risk for sepsis that may be related to hepatic fibrosis and ascending cholangitis. The utility of early liver transplantation in ARPKD patients with significant hepatobiliary disease is discussed.

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Childhood PKD encompasses the diagnoses of ARPKD, ADPKD, GCD, and syndromes such as tuberous sclerosis or Jeune's syndrome. According to the European Dialysis and Transplant Association, 7% of children less than 2 yr of age and 10% of children 2–15 yr of age requiring renal replacement therapy between 1976 and 1989 were diagnosed with PKD (1). In the most recent report of NAPRTCS, 3% of children underwent renal tranplantation for ESRD secondary to PKD (2). Cole and colleagues assessed the natural history of PKD in children diagnosed before 1 yr of age and who survived the first month of life (3). They found that 83% of children with ESRD secondary to PKD were diagnosed with ARPKD compared with 17% with a diagnosis of ADPKD. The age at diagnosis of ESRD among the ARPKD patients ranged from 0.7 to 16.4 yr compared with 3.5 yr in a single ADPKD patient. Therefore, natural history studies assessing the

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CHF, congenital hepatic fibrosis; ESRD, end-stage renal disease; GCD, glomerulocystic disease; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; PKD, polycystic kidney disease.

long-term prognosis of PKD patients following renal transplantation must focus on issues related to the morbidity and mortality of ARPKD.

Although several studies reveal a favorable long-term prognosis for neonatal survivors with ARPKD (4, 5), hepatobiliary disease secondary to CHF and biliary dysgenesis, which are constant findings in ARPKD, may potentially impact the overall morbidity and mortality of ARPKD patients (4–6). Overt clinical manifestations of hepatobiliary disease such as hepatic enlargement or increased echogenicity on ultrasound, esophageal varices, enlargement of the spleen, or ascending cholangitis, occur in 46–83% of children (4, 5). Approximately 50–60% of ARPKD patients develop significant portal hypertension that may require placement of a portosystemic shunt (4, 5, 7). As hepatocellular dysfunction is usually mild, liver transplantation because of hepatocellular failure is required infrequently (4, 5, 8, 9).

Long-term studies in adults with ADPKD demonstrate similar patient and graft survivals compared with non-ADPKD patients following renal transplantation (8, 9). However, comparable studies in children with PKD are limited to small single center reports of ADPKD patients (4, 5, 10).

Therefore, the aims of this study are: (i) To determine if patient and graft survival rates following renal transplantation are similar in children with PKD compared with controls; (ii) To determine whether survival of ARPKD patients following renal transplantation is adversely affected by hepatobiliary disease complications such as sepsis associated with ascending cholangitis or gastrointestinal bleeding.

Methods

Using the NAPRTCS registry, we identified patients undergoing renal transplantation between January 1987 and December, 2001 with an ESRD diagnosis of PKD. The methods employed by NAPRTCS have been previously reported (2). Briefly, NAPRTCS is composed of 145 participating medical centers from the USA, Canada, Mexico, and Costa Rica. Each NAPRTCS center has a principal investigator, associate investigators, and data coordinators. Participating centers voluntarily submit data on a regular basis regarding children and adolescents who have received a renal transplant (since 1987), who are undergoing dialysis (since 1991), and those with chronic renal insufficiency (since 1994). Renal transplant recipient data are derived from 73 centers, which collect information at the time of transplantation, on day 30 post-transplant, and every 6 months thereafter.

Deceased PKD patients, all with a diagnosis of ARPKD, were further identified and characterized using a special questionnaire submitted to the principal investigators. The diagnosis of ARPKD was substantiated according to a modification of the criteria of Zerres and colleagues (4, 11) by either a characteristic appearance on renal ultrasound, pathologic confirmation, presence of congenital hepatic fibrosis, or absence of renal cysts in both parents. General information regarding gender, age at transplantation, retransplantation, age at death, cause of death, and death with a functioning graft was obtained. In addition, we performed a case-control (1:3) study comparing the length of post-transplant survival in deceased ARPKD and non-PKD patients matched for gender, age, race, transplant year, prior transplant, and donor source. Hepatic status within 1 yr of death was assessed for the presence of splenomegaly, hepatomegaly or ascites, upper and lower gastrointestinal bleeding, need for treatment of portal hypertension, history of cholangitis, and need for liver transplantation.

Standard univariate and multivariate statistical methods were used for data analysis. Kaplan–Meier product limit estimates of graft survival and acute rejection episodes were constructed and tested using the log-rank test. Relative risks of graft failure, acute rejection, and survival beyond 3 yr following renal transplantation were derived from Cox proportional hazards regression models. Mean ($\pm$s.d.) were expressed for patient age at transplant, age at death, and interval from age at transplant to age at death.

Results

During the study period, 203 patients with an ESRD diagnosis of PKD underwent 225 renal transplants and 7044 non-PKD patients underwent 7725 renal transplants. Compared with non-PKD patients, PKD patients tended to undergo renal transplantation at a younger age (8 ± 5.5 vs. 11 ± 5.2 yr, $p < 0.001$) and were more likely to be Caucasian (77% of PKD vs. 62% of non-PKD patients, $p < 0.001$). Overall graft (Fig. 1) and patient (Fig. 2) survival rates were not significantly different between PKD and

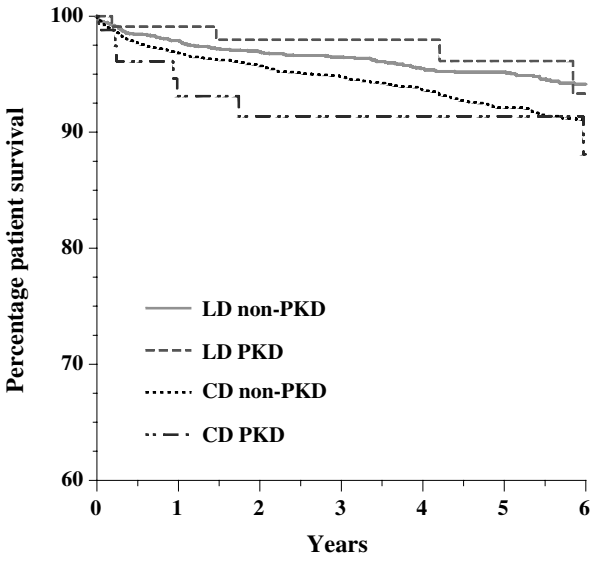

Fig. 1. Patient survival rate of PKD patients and non-PKD patients following renal transplantation. CAD, cadaveric; LD, living donor.

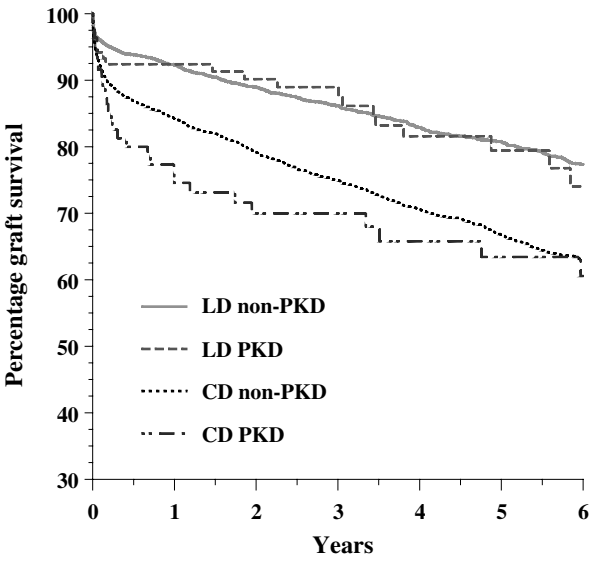

Fig. 2. Graft survival rate of PKD patients and non-PKD patients following renal transplantation. CD, cadaveric; LD, living donor.

non-PKD patients and did not vary by donor source. No differences in rates of acute rejection or time to first rejection were noted between PKD and non-PKD patients.

Four hundred sixty two deaths (6.5%) occurred in the non-PKD patients. The causes of death included infection (32%), cardiopulmonary disease (16%), cancer (11%), hemorrhage (8%), other (28%), and unknown (5%).

Fourteen deceased patients, all with an ESRD diagnosis of ARPKD, were identified within the PKD group and are summarized in Table 1. The mean ages at time of transplant and time of death were 4.9 ± 4.5 and 8.7 ± 4.9, respectively. The mean interval from the last transplant to death was 3.3 ± 3.0 yr. The relative risk of living longer than 3 yr in the deceased ARPKD patients compared with deceased non-PKD patients was not significant (RR = 0.70, p = 0.28). Sepsis was identified as a likely factor in the cause of death in nine (64%) patients and was comfirmed with a positive blood culture in four patients. One patient demonstrated positive blood cultures that were definitively associated with ascending cholangitis. Ten of 14 patients died with a functioning renal allograft.

The hepatic status of these patients is summarized in Table 2. Both patients (no. 1 and 7) undergoing either orthotopic liver transplantation or combined cadaveric kidney–liver transplantation died within 2 months of the procedure. One patient (no. 9) died awaiting a combined kidney–liver transplant as the result of presumed sepsis.

Discussion

Despite being transplanted at a younger age, our results demonstrate that PKD and non-PKD transplant recipients have similar rates of patient survival, graft survival, and acute rejection. Therefore, the ESRD diagnosis of PKD does not pose a graft survival disadvantage as noted with other diagnoses such as focal segmental glomerulosclerosis and congenital nephrotic syndrome (12).

Although our results are limited by an inability to either determine the exact distribution of ARPKD, ADPKD, GCD, and syndrome-associated PKD in the NAPRTCS patient population studied or to substantiate the diagnosis of PKD in all patients, the data by Cole et al. (3) would suggest that most of our patients had ESRD

Table 1. Summary of deceased ARPKD patients

Patient no.	Gender	Age at TX (yr)	Age at death (yr)	Cause of death	Functioning graft
1	F	9.4	15.3	PTLD/candidal sepsis/aspergillosis	Y
2	M	3.3	11.7	PTLD	Y
3	F	1.7	7.6	Bacterial sepsis	Y
4	F	1.8/5.2	8.3	Bacterial sepsis	Y
5	F	7.5	7.7	Cardiac arrest/probable sepsis	Y
6	M	18.8	20.3	MVA	Y
7	F	4.2	12.4	Hepatic failure	Y
8	F	1.3	2.2	Cardiac arrest/probable sepsis on PD	N
9	F	5.3	6.0	Probable sepsis	N
10	F	4.7	4.7	Bleeding complication from CL placement	Y
11	M	9.2	10.9	Bacterial sepsis/ascending cholangitis	Y
12	F	1.7/2.0	5.9	Bacterial sepsis	N
13	F	1.7	7.6	PTLD; sepsis	Y
14	M	1.0	1.2	Viral sepsis	N

F, female; M, male; TX, transplant; PTLD, post-transplant lymphoproliferative disease; MVA, motor vehicle accident; PD, peritoneal dialysis; CL, central line; Y, yes; N, no.

Table 2. Hepatic disease among deceased ARPKD patients

Patient no.	Splenomegaly	Hepatomegaly	GI bleed	Portal hypertension treatment	Cholangitis	Ascites	Other
1	Y	Y	N	Banding	Y	Y	Orthotopic LTx 2 months prior to death
2	NA	NA	NA	NA	NA	NA	
3	Y	Y	N	None	NA	NA	Portal HTN present
4	Y	Y	N	Renosplenic shunt/sclerotherapy	N	Y	Factor VII def, lupus inhibitor
5	Y	N	N	Splenectomy	N	N	E-G varices
6	N	N	N	None	N	N	
7	N	Y	N	None	Y	Y	Combined K/LTx complicated by HA thrombosis
8	N	N	N	None	N	N	
9	Y	Y	Y	Sclerotherapy	N	Y	E/G varices; S/P splenectomy; died awaiting K-LTx
10	N	Y	N	None	N	Y	
11	Y	Y	N	TIPS	Y	Y	
12	Y	Y	Y	None	N	Y	UGI bleed
13	Y	Y	N	None	N	N	
14	N	N	N	None	N	N	

Y, yes; N, no; GI, gastrointestinal; NA, data not available; TIPS, transjugular intrahepatic portosystemic shunt; L, liver; Tx, transplant; HTN, hypertension; Def, deficiency; E-G, esophageal-gastric; K, kidney; HA, hepatic artery; S/P, status post; UGI, upper gastrointestinal.

secondary to ARPKD. This suggests that ARPKD patients have a favorable graft and patient survival following successful renal transplantation. Furthermore, our patient survival rates were slightly better than Khan and associates who reported 1 and 5 yr patient survivals of 93 and 86%, respectively, in a single center report of 14 ARPKD patients followed for a mean of 14.5 yr (range 3–34 yr) (10). The relatively low frequency of gastrointestinal bleeding complications in our deceased PKD patients may be because of their younger age as bleeding complications from esophageal varices are more likely to occur in the second decade of life (5).

Several single-center reports describe the long-term follow-up of ARPKD patients undergoing renal transplantation and the impact of hepatobiliary disease on patient survival. Khan et al. described the long-term hepatic complications seen in a group of pediatric renal transplant recipients with ARPKD (10). In this single center report of 14 patients, hypersplenism, esophageal varices with gastrointestinal bleeding, and bile duct dilatation were seen in 50, 36, and 36% of patients, respectively, transplanted at a mean age of 8.3 yr (range 1–22 yr) and followed for a mean period of 14.5 yr. Complications related to CHF including sepsis/cholangitis (n = 3) and hepatic failure (n = 1) were directly responsible for death in 29% of ARPKD patients following renal transplantation. Although Roy et al. noted significant liver disease in three of seven renal transplant recipients at a median follow-up age of 17.5-yr-old, no deaths were attributed to complications from hepatic disease (5). No deaths were reported by Zerres (4) or Jamil (13) among eight patients undergoing renal transplantation.

We noted a relatively high rate of presumed sepsis as the cause of death among 14 ARPKD patients. It is unclear whether these results are because of a general phenomenon in pediatric renal transplant recipients or is specifically related to the presence of hepatic dysfunction in the ARPKD patient. For example, Denny et al. (14) noted that sepsis accounted for 44% of deaths in children receiving a renal transplant who died before 18 yr of age compared with a rate of 19% in recipients who died after 18 yr of age. Similarly, Seikaly and colleagues reported that bacterial infections and cardiopulmonary events were the two leading causes of death within the NAPRTCS registry of over 6500 renal transplant recipients (2). On the other hand, bacterial cholangitis occurs in 10–20% of children with isolated or ARPKD-associated CHF (15, 16) and is fatal in approximately 1% of children with ARPKD (5, 17). In a recent study, recurrent bacteremia and sepsis because of enteric pathogens associated with suspected or documented cholangitis was reported in eight ARPKD patients on dialysis (n = 5) or after renal transplantation (n = 3) (18). In this study, all three transplant recipients had a history of fevers or bacteremic episodes prior to transplantation and recurrent infections in the post-transplant period directly contributed to allograft failure in two patients. Finally, recurrent cholangitis was noted in a 25-yr-old transplant recipient in the report by Jamil (13).

Infectious cholangitis usually develops in the presence of an infected and obstructed biliary tract system (19). Patients with congenital hepatic fibrosis are pre-disposed to bacterial superinfection of the bile because of sludging and trapping of bile within abnormal immature bile

ducts that are slowly being destroyed by the underlying cholangiopathy. Infected bile and increased intraluminal pressure frequently leads to bacteremia which can progress to septic shock and death (19). The influence of immunosuppressive agents on the immune processes governing the colonization and replication of bacteria in bile is unknown.

No definitive guidelines exist regarding the proper management of portal hypertension and end-stage liver disease in ARPKD patients. The importance of developing appropriate guidelines is illustrated by the fact that three of the deaths in our patient population occurred in patients immediately following or awaiting liver transplantation. Standard therapies for prevention of hemorrhagic complications related to portal hypertension include use of β-adrenergic antagonists, placement of splenorenal or transjugular intrahepatic portosystemic shunts, and endoscopic sclerotherapy or banding (20, 21). Placement of a portosystemic shunt in patients with end-stage renal disease on dialysis should be done with caution as these patients are at risk for hepatic encephalopathy because of an inability to properly excrete ammonia (22). Furthermore, portosystemic shunts may need to be revised because of thrombosis or growth of the child. Selection of the proper type of shunt depends on the child's vascular anatomy and the need to preserve the integrity of the inferior vena cava for future transplantation. Although appealing as a temporizing solution, transjugular shunts should only be carried out while awaiting liver transplantation because of a much higher risk of thrombosis.

Therefore, simultaneous or sequential liver and kidney transplantation, which has been performed in a limited number of ARPKD patients, may be a more reasonable therapeutic option if performed preemptively prior to developing end-stage liver or kidney disease (23, 24). Liver transplantation is particularly appealing today because of significant improvements in patient survival over the past decade (25).

Despite the retrospective nature of this study and the relatively small number of reported deaths of ARPKD patients, we believe our results emphasize a critical clinical issue in the management of patients with childhood PKD patients requiring renal transplantation. Although children are at risk for developing sepsis following renal transplantation (2, 14), ARPKD transplant recipients appear to be at increased risk for sepsis that may be related to hepatic fibrosis and ascending cholangitis. Post-transplant antibiotic prophylaxis with drugs such as trimethoprim-sulfamethoxazole, as suggested by Kashtan et al. (18), is supported by our data and should be considered as standard therapy in the post-transplant period. Furthermore, sequential or simultaneous liver-kidney transplantation may need to be performed earlier than previously considered. Liver transplantation should be viewed as a viable therapeutic alternative to portosystemic vein shunting procedures, particularly in the presence of end-stage renal disease. We recommend further prospective multicenter studies to assess the safety and effectiveness of these therapeutic strategies.

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