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ORIGINAL ARTICLE

Combined liver-kidney transplantation for children with autosomal recessive polycystic kidney disease (ARPKD): indication and outcome

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Abstract

In ARPKD, mutations in the *PKHD1* gene lead to remodeling of the kidneys and liver. These may result in progressive liver fibrosis with portal hypertension requiring combined liver and kidney transplantation (CLKT). There is currently no consensus on the indication for CLKT and data on long-term outcomes are scarce. We analyzed in detail the pretransplant liver symptomatology, laboratory and ultrasound data, histological studies, and genotypes in eight patients undergoing CLKT. The median age was 10.1 years (range 1.7–16) and median follow-up was 4.6 years (range 1.1–8.9). All patients had clinical signs of portal hypertension and abnormal ultrasound findings. Congenital hepatic fibrosis was present in all pretransplant biopsies (6 out of 8 patients) and in all explanted livers. All patients survived; liver and kidney graft survival was 72% and 88%, respectively. Liver and kidney function were stable in all patients with a median eGFR of 70 ml/min/1.73 m² (range 45–108 ml/min/1.73 m²). Height-SDS improved significantly after 12, 24, and 36 months ($P = 0.016$, 0.022 and 0.018 respectively). The indication for CLKT remains challenging and controversial. A favorable outcome for patients with ARPKD can be achieved by using the degree of portal hypertension, longitudinal ultrasound examinations, and preoperative liver histology as parameters for CLKT.

Introduction

Autosomal recessive polycystic kidney disease (ARPKD), is the most common ciliopathy in children, with a frequency of approximately 1 in 20 000 live births [1,2]. Most patients have mutations in the polycystic kidney and hepatic disease 1 (*PKHD1*) gene that encodes fibrocystin/polyductin [3,4]. The clinical spectrum of ARPKD varies widely and includes liver and kidney involvement [5]. Renal involvement ranges from a urinary concentration defect in apparently normal kidneys to enlarged cystic kidneys. Most patients have fusiform dilatations of the renal collecting ducts leading to a progressive renal insufficiency and the need for renal replacement therapy [5,6].

In the liver, defective remodeling of the ductal plate, abnormal portal veins, and progressive fibrosis of the portal tracts occur [6]. These histological changes lead to severe portal hypertension, splenomegaly with hypersplenism, and

bleeding complications because of esophageal varices. In addition, congenital hepatic fibrosis predisposes to recurrent cholangitis.

Early results of isolated kidney transplantation were dominated by high mortality, mainly because of severe recurrent cholangitis [7–9]. Ueno *et al.* [10] reported that patients with good renal function prior to receiving an isolated liver graft are at greater risk of developing end-stage renal failure in the further course. One-third of the patients of this study required renal replacement within 4 years.

Combined liver and kidney transplantation (CLKT), is a reasonable approach [8,9,11], but outcome data are scarce, especially in children. Two studies reporting data from adult patients showed a good outcome with survival rates of 75% [10,12]. Perera *et al.* [13] reported a series of children undergoing CLKT for ARPKD with 4 deaths out of 14 patients (survival rate of 71%). In three patients, death was directly related to the liver or kidney transplantation.

In addition to this, there is currently no consensus as to when CLKT should be performed, mainly because liver synthesis is often preserved for a long time [14,15].

Our center is a major referral center for patients with CLKT including ARPKD. In this report, we systematically review the decision-making process for CLKT for patients with ARPKD with special attention to clinical symptoms, histological changes in the affected organs and genetic data and we present long-term results of postoperative outcomes including growth.

Patients and methods

Study design

We conducted a retrospective chart analysis of a selected group of eight children with ARPKD who underwent CLKT at the University Medical Center Hamburg-Eppendorf.

Pretransplant hepatic and renal phenotypes were analyzed using routine laboratory data, color Doppler ultrasound examinations of liver, kidney and spleen, histological results of liver biopsies and genetic findings. To critically review the process of decision-making for CLKT, we investigated the histological hepatic phenotype (pretransplant liver biopsies in six patients, and histology of the explanted organs in all eight cases). Postoperative outcomes were recorded, including organ function and complications. To describe long-term outcomes we analyzed longitudinal routine laboratory and clinical data including longitudinal growth data.

Doppler ultrasound

All Doppler ultrasound examinations were performed by the same experienced pediatric radiologist (K.H.) using a commercial scanner (HDI 5000 SonoCT; Philips Medical Systems, Best, the Netherlands) with a high-resolution 12-5-MHz linear-array transducer (L12-5, 50 mm; ATL Ultrasound, Bothell, WA, USA) and a 7-4-MHz curved-array probe (C7-4 40R; ATL Ultrasound). Liver length was measured in the longitudinal scan in the mid-clavicular plane and spleen length was measured on the coronal view between the most superomedial and the most inferolateral points.

Growth

Growth was measured as height expressed as a standard deviation score (SDS) and was analyzed longitudinally. Paired Student's *t*-test were used to analyze significant differences between pretransplant SDS and the SDS at 12, 24, and 36 months of follow-up after transplantation.

Immunosuppression

As previously reported [16], immunosuppression was based on an induction therapy with two single doses of basiliximab (Simulect®; Novartis Pharma GmbH, Basel, Switzerland) on day 1 and day 4 post-transplant and prednisolone, mycophenolate mofetil, and cyclosporine A for maintenance of immunosuppression.

Genetics

We performed direct sequencing of the entire coding region of the *PKHD1* gene including exon-intron boundaries (GenBank: NM_138694.3; mutation numbering + 1 corresponds to the A of the ATG-translation initiation codon). The patients' genomic DNA was amplified by PCR with oligonucleotide primers complementary to flanking intronic sequences (primer sequences and PCR conditions are available on request). PCR products were sequenced employing ABI BigDye chemistry (Applied Biosystems, Darmstadt, Germany). The same primers as for PCR were used as sequencing primers. Samples were run and analyzed on an ABI PRISM 3130 genetic analyzer (Applied Biosystems). Scoring of likely mutations was performed as described previously using a multiple sequence alignment of orthologs and different bioinformatic algorithms [17].

Results

Eight children (five males) with ARPKD received a CLKT at the University Medical Center Hamburg-Eppendorf since 2003. The median age at transplantation was 10.1 years (range 1.7–16 years) and the median body weight was 25.1 kg (range 10.5–58 kg). Median follow-up duration at the time of the study was 4.6 years (range 1.1–8.9 years).

Pretransplant renal phenotype

Before transplantation, five children had end-stage renal disease (ESRD) with a median duration of 1.7 years (range 0.2–2.1 years) and required renal replacement therapy. Three patients were treated with peritoneal dialysis and two patients underwent hemodialysis. In the youngest patient (P6) with congenital ESRD, both kidneys were explanted before the age of 6 months to allow peritoneal dialysis.

Three patients (P2, P3 and P4) had CKD stage 4 with calculated GFRs [18] of 24, 21 and 20 ml/min/1.73 m², respectively. Ultrasound examinations showed typical results for ARPKD, with enlarged hyperechogenic cystic kidneys with poor cortico-medullary differentiation.

Pretransplant hepatic phenotype

All patients suffered from portal hypertension with hypersplenism. Five patients had leukocytopenia and thrombocytopenia at the time of transplant. Esophageal varices where present in 3 patients, and one patient's course was complicated by severe bleeding from varices. One patient (P3) had recurrent cholangitis that required antibiotic treatment.

Liver synthesis was normal in all patients and transaminases were minimally elevated at the time of the study. Median aspartate aminotransferase and alanine aminotransferase levels, were 31 U/I (range 17–49 U/I, normal value 10–35 U/I) and 25 U/I (range 15–38 U/I normal value 10–35 U/I), respectively. The median prothrombin time was 99.4% (range 87.4–108%, normal value 80–130%).

Doppler ultrasound examinations of the liver were abnormal in all patients with enlarged hyperechogenic organs and signs of portal hypertension together with splenomegaly. Seven patients showed reduced or retrograde flow in the portal vein. Detailed information is given in Table 1.

In six patients, a percutaneous liver biopsy was performed prior to transplantation. We did not perform a percutaneous liver biopsy in one patient on peritoneal dialysis (P6) and in two patients who presented with severe bleeding from varices, typical ultrasound findings of decreased flow in the hepatic artery and retrograde flow in the portal vein (P8). Histology of pretransplant biopsies of the liver showed septal fibrosis with typical signs of congenital fibrosis and partial development of cirrhosis (Tables 1 and 2).

Histological results of the explanted organs

In five patients, nephrectomy was performed prior to transplantation or during the operation for CLKT. In all cases, cystic remodeling of the kidneys and scarring of the nephrons was found.

Histology of the explanted livers revealed typical signs of advanced liver fibrosis of the ARPKD type (Fig. 1b–e). Livers of all cases presented intense and broad septal fibrosis (Fig. 1b and d). The extent of fibrotic areas varied. Semi-quantitative evaluation of liver sections (Table 2) revealed mean values of about 30–60% fibrotic areas per section. In most patients, hepatocyte-containing tissue revealed a varied mixture of lobular and pseudo-lobular nodules without central veins (Fig. 1b), indicating different degrees transition from fibrosis to cirrhosis. Fibrotic septa in all patients had significantly reduced numbers and diameters of the peripheral branches of portal veins (Fig. 1d). Septa also contained greatly augmented small bile ducts, which were mainly oriented in multiple circular, often branched layers in the position of ductal plates (Fig. 1c and d). In addition, all cases had a normal or increased number of larger interlobular bile ducts, centrally located in the septa; these were mainly dilated and often branched with the knob-like intraluminal protrusions typical of ARPKD (Fig. 1b). Cholestasis was mainly limited to intraductular bile deposits without significant intralobular cholestasis. Cholangitis was only present in three patients. The most important histological parameters of hepatic alterations are summarized for the individual patients in Tables 1 and 2.

Clinical outcome – kidney and liver graft function after transplant

Data on the prognostic factors and outcomes of immediate pediatric intensive care treatment and complications have been published in part previously [16]. Patient survival was 100% after a median follow-up of 4.6 years and all patients were doing well. Liver and kidney graft survival was 72% and 88%, respectively. The first patient (P1) had to be given a liver and kidney retransplantation secondary to renal artery thrombosis and acute liver failure on day 3. A liver retransplantation on day 5, was necessary because of primary nonfunction. After 2 years the retransplanted kidney graft failed because of nonadherence, and renal replacement treatment was re-started. A third kidney transplantation was peformed after transferring the patient to the adult department after 3.5 years of hemodialysis.

In another patient (P7), liver retransplantation was necessary after 3 months because of hepatic vein stenosis with chronic graft failure and refractory ascites. The most recent median serum creatinine level was 0.75 mg/dl (range 0.36–1.57 mg/dl), resulting in a calculated median GFR of 70 ml/min/1.73 m² (range 45–108 ml/min/1.73 m²) using the new Schwartz formula from 2009 [19]. Longitudinal GFR values for each patient are shown in Fig. 2.

Arterial hypertension requiring medical treatment was present in six patients, at the time of the study. All patients needed double or triple antihypertensive medication. Liver function was stable in all patients at the end of the study.

Table 1. Clinical hepatic phenotype and post-transplant histological results of the explanted organs.

	Pretransplantation			Histology of explanted organs		Transplantation	
	Clinical hepatic phenotype	Ultrasound/color Doppler	Liver biopsy	Liver	Kidney	Age at Tx (years)	Type of graft (segments)
P1	Portal hypertension	Liver 14.7 cm, spleen 16.4 cm, micro nodular remodeling of liver, reduced orthograde flow in portal vein, decreased enddiastolic liver perfusion, increased flow velocity in hepatic artery	Cholangiodysplastic pseudocirrhosis, proliferation of bile ducts, pseudo-lobular remodeling of liver tissue, cholestasis	1728 g, 29 cm × 18 cm × 10 cm, complete nodular remodeling of the liver, hepatic fibrosis with cystic bile duct malformation and multiple ectopic sites of intrahepatic pancreatic tissue	Results not available	12.8	Whole graft
P2	Portal hypertension, esophageal varices	Liver 12.6 cm, spleen 14.3 cm, irregularity of the liver echogenicity, reduced arterial perfusion of liver	Complete micronodular pseudo-lobular remodeling of the liver tissue	1960 g, 23 cm 16.5 cm × 9 cm, cholangiodysplastic pseudocirrhosis of the liver with moderate cholestasis, complete micronodular remodeling of the parenchyma, branched and cystic bile ducts, proliferated bile ducts	No nephrectomy performed	15.9	Split [1,4–8]
P3	Portal hypertension, recurrent cholangitis	Liver 12.9 cm, spleen 11.2 cm, irregularity of the liver parenchyma, increased echogenicity, retrograde flow in the portal vein, many collaterals, ascites	Septal fibrosis, proliferation of bile ducts, cystic bile ducts, no signs of cholangitis	1404 g, 20.5 cm × 17 cm × 9 cm severe cholangio-dysplastic hepatic fibrosis with branched and cystic bile ducts, little sign of chronic cholangitis	Right kidney: 556 g, 17 cm × 8 cm × 8 cm subtotal polycystic remodeling, extensive scarring of the few noncystic nephrons	4.1	Split [2,3]
P4	Portal hypertension, esophageal varices, hypersplenism, pancytopenia	Liver 13.7 cm, spleen 15 cm, irregular liver parenchyma, increased echogenicity, normal perfusion	Septal fibrosis with partial cirrhosis	1780 g, 26 cm × 19 cm × 9 cm congenital hepatic fibrosis with complete micronodular remodeling of parenchyma	No nephrectomy performed	10.1	Whole graft

Table 1. continued

	Pretransplantation			Histology of explanted organs		Transplantation	
	Clinical hepatic phenotype	Ultrasound/color Doppler	Liver biopsy	Liver	Kidney	Age at Tx (years)	Type of graft (segments)
P5	Portal hypertension, hypersplenism, hypogammaglobulinemia	Liver 10.5 cm, spleen 16 cm, irregular liver parenchyma, increased echogenicity, decreased portal perfusion	Advanced septal fibrosis, no cholestasis	1188 g, 21 cm × 18 cm × 8.5 cm advanced polycystic liver disease with septal fibrosis, moderate focal secondary cholestasis	Right kidney: 413 g, 15 cm × 7 cm × 9.5 cm, complete polycystic kidney disease, maximal cyst diameter 1.2 cm	10.1	Split [2,3]
P6	Portal hypertension, ascites, leukopenia	Liver 8.5 cm, spleen 7 cm, Irregular iver parenchyma, increased echogenicity, decreased portal perfusion	No biopsy performed	645 g, 17.4 cm × 12.5 cm × 6.8 cm complete septal fibrosis	Left kidney: (explantation at the age of 2 days): 213 g, 10.2 cm × 7.3 cm × 6 cm cystic formation of almost all nephrons right kidney: (explantation at the age of 6 months): 1180 g, 17 cm × 12 cm, cystic formation of almost all nephrons, secondary oxalate crystals	1.7	Whole graft
P7	Portal hypertension, leukopenia	Liver 10.8 cm, spleen 9.5 cm, irregular liver parenchyma, increased echogenicity, rounded margins, decreased end-diastolic perfusion	Advanced septal fibrosis (grade 3 of 4) with congenital dysplasia of bile ducts, secondary cholestasis	1202 g, 20 cm × 14 cm × 10 cm complete septal fibrosis with distinctive cholangioductal dendritic formation of cysts, cholestasis	Right kidney: 202 g, 11 cm × 7 cm × 5.5 cm complete polycystic remodeling of the parenchyma	6.6	Split [2,3]
P8	Portal hypertension, esophageal varices, bleeding from varices hypersplenism, leukopenia, thrombocytopenia	Liver 13.5 cm, spleen 14.9 cm, irregular liver parenchyma, increased echogenicity, small cysts, rounded margins	No biopsy performed	1850 g, 22 cm × 17.5 cm × 10.5 cm micronodular cirrhosis, severe cholestasis	No nephrectomy performed	15.0	Whole graft

Table 2. Synopsis of relevant histological parameters in explanted livers for the individual patients.

	Fibrosis type 1 = portal 2 = septal 3 = cirrhosis (approx.% of fibrotic tissue in section area)	Portal veins (peripheral branches): r = reduced *n* = normal d = dilated	Peripheral bile ducts (ductal plate area): 0 = reduced 1 = normal 2 = slightly increased 3 = significantly increased b (+/++) = branched d (+/++) = dilated	Central (interlobular) bile ducts: 0 = reduced 1 = normal 2 = slightly increased 3 = significantly increased b (+/++) = branched d (+/++) = dilated	Cholestasis (histologically visible bile deposits): 0 = absent 1 = slight 2 = intense D = ductal L = intralobular	Cholangio-ductular metaplasia (CK7 positivity) of hepatocytes 0 = absent 1 = slight 2 = intense	Cholangitis 0 = absent 1 = slight 2 = intense
P1	3 (40)	r	3 b++, d+	1 b++, d++	1 D	0	0
P2	2–3 (40)	r	3 b++, d++	1 b++, d++	1 D	0	0
P3	3 (30)	r	3 b+ d+	1 b+, d+	0	0	1
P4	3 (30)	r	3 b++, d+	1 b++, d+	1 D	0	1
P5	2–3 (50–60)	r	3 b++, d++	1 b++, d++	1 D	0	0
P6	2 (30)	r	3 b++, d++	1 b++, d++	1 D	0	0
P7	3–2 (40)	r	3 b++, d++	1 b++, d++	2 D	0	1
P8	3–2 (30–40)	r	3 b++, d++	1 b++, d++	2 D	0	0

Coagulation tests were normal in all patients [median Quick value 105% (range 86–120.1), median International Normalized Ratio, INR value 1.02 (range 0.9–1.1)].

Long-term complications

In two patients, a ureterocystoneostomy was performed because of high-grade vesicoureteral reflux into the kidney graft and recurrent febrile urinary tract infections. Patient P3, could not be weaned off steroids because of slightly elevated liver function values. Patient P4, was switched from cyclosporine to tacrolimus because of hypertrichosis.

Longitudinal growth

Pretransplant SDS had a median value of −2.2 (range −1.0 to −3.1). After 12 months (median SDS −1.4), 24 months (median SDS −1.4), and 36 months (median SDS −1.3) of follow-up, CLKT growth SDSs improved significantly ($P = 0.016$, 0.022 and 0.018 respectively).

Genetics

PKHD1 mutation analysis was performed in all, but one of our patients. Mutations were found to be scattered throughout the gene without evidence of clustering at specific sites. In patient P5, heterozygosity was demonstrated for the most frequent *PKHD1* mutation, c.107C > T (p.Thr36Met), but a second change was not detected. Although two *PKHD1* mutations can be expected in an autosomal recessive disorder such as ARPKD a diagnosis of ARPKD in this patient is most likely given the character of the identified mutation, the patient's clinical features, and the overall low allele frequency in the normal population. In all other patients, at least two mutations were identified. Although parental DNA samples were not available for analysis except for one pedigree, we hypothesized that the detected changes were located *in trans* on different parental alleles in compound heterozygous state. All of our mutations were predicted *in silico* by different bioinformatic tools with probable pathogenic relevance or were previously shown to affect residues that are essential for fibrocystin/polyductin function (Table 3).

Discussion

This is the first study to present comprehensive data on pretransplant hepatic and renal phenotype, genotype and post-transplant outcomes of children with ARPKD who have been referred for evaluation of CLKT. Although liver synthesis was maintained in our patients even with distinct clinical symptoms, disorders such as portal hypertension were present in all patients, leading to gastrointestinal bleeding in a significant subset. Histological findings before and after CLKT confirmed substantial hepatic pathology in this cohort of ARPKD patients. Our single-center experience documents a favorable outcome with 100% patient survival and significantly improved growth after CLKT for this cohort.

Indication

Making a decision for kidney transplantation in ARPKD is relatively straightforward. The renal phenotype is easy to follow up and renal replacement therapy was often initiated at the time of transplant, although in three patients we opted for a pre-emptive transplantation and performed CLKT at CKD stage 4 with a GFR of around 20 ml/min/1.73 m².

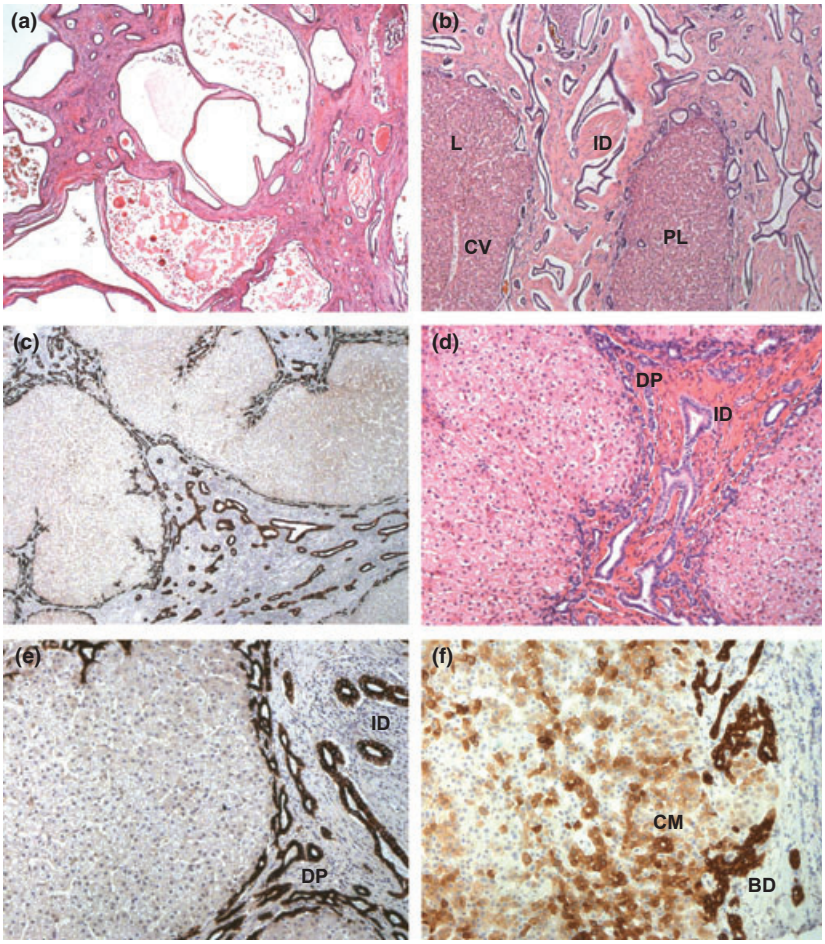

Figure 1 Histological results of the explanted organs of patients with ARPKD receiving a combined liver-kidney transplantation. (a) Kidney explant in ARPKD (P 3) with advanced multicystic malformation (H&E). (b–d) Liver explants in ARPKD (b = P5, c + d = P3): advanced septal fibrosis with transition to cirrhosis: lobule (L) with persistent central vein (CV) on the left side; pseudo lobule (PL) without central vein on the right; markedly reduced peripheral branches of portal veins in septa; preserved but dilated and branched interlobular bile ducts (ID); increased number of elongated bile ductules arranged in multiple circular layers in the area of the ductal plate (DP). (b and d) H&E; (c) immunohistochemical labeling for cytokeratin 7 (=CK7) with dark brown staining of bile ducts and ductulus). (e) Liver in ARPKD (P3): immunohistochemical labeling for CK7: negative staining of hepatocytes indicating absence of cholangiocellular metaplasia of hepatocytes. (f) For comparison: positive CK7 staining of many hepatocytes in a case of secondary biliary cirrhosis in primary sclerosing cholangitis (PSC) indicating presence of significant cholangiocellular metaplasia of hepatocytes in other types of progressing chronic cholestasis. L, hepatic lobule; PL, hepatic pseudolobule; ID, interlobular bile duct; CV, central vein; DP, ductal plate; BD, bile ducts; CM, cholangiocellular metaplasia of hepatocytes.

However, there are few data with regard to the optimal liver transplantation strategy for patients with ARPKD. In patients with ESRD and a minor degree of liver disease, single kidney transplantation (KTx) is feasible.However, these patients need to be examined regarding their liver phenotype, with serial ultrasound examinations and liver biopsy pretransplantation if in doubt. Sepsis because of ascending cholangitis should be kept in mind as a possible severe complication after KTx. Khan *et al.* reported a 50% mortality rate after isolated kidney transplantation for ARPKD because of recurrent cholangitis in adults [7] and Davis *et al.* reported the same phenomenon in a pediatric cohort derived from the NAPRTCS registry [8].

In a small subset of patients with ARPKD renal function, is preserved and liver involvement is the leading clinical symptom. In this case, an isolated liver transplantation can be considered, but only 30 patients in this situation have been described in the literature so far [15]. Notably, seven of these patients died because of cholangitis and sepsis. This shows that even after isolated LTx, we need to be aware of complications related to ARPKD. It is well known that with mild chronic kidney disease in

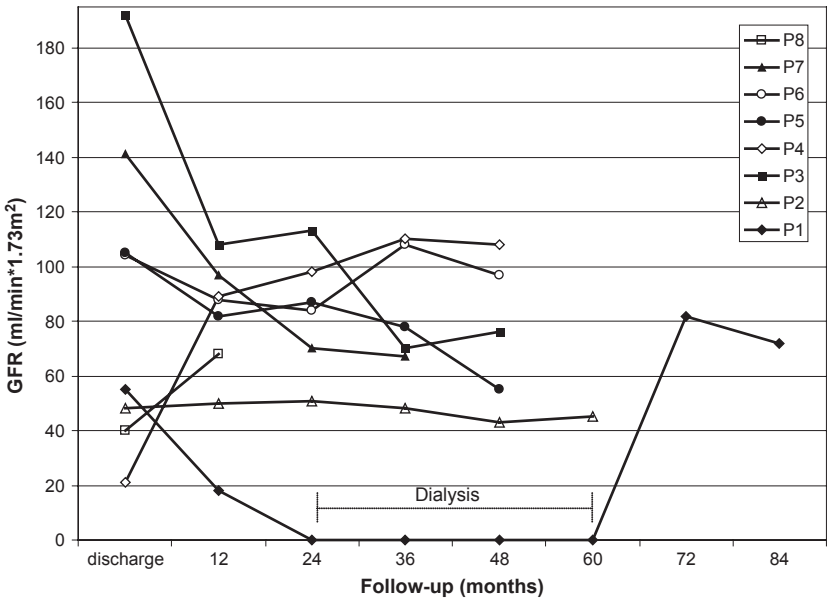

Figure 2 Longitudinal course of glomerular filtration rate (GFR) after combined liver and kidney transplantation for ARPKD.

addition to severe liver involvement, immunosuppression may lead to deterioration of renal function with KTx needed after LTx. However, Arikan *et al.* reported beneficial effects of LTx on renal function for ARPKD [20]. Our own experience is that dealing with immunosuppression after an isolated liver transplantation while performing renal replacement therapy can be challenging, and runs the risk of severe infection because of the necessary dialysis catheter [21].

In the case of portal hypertension and liver fibrosis in combination with ESRD, a portosystemic shunt prior to KTx or CLKT has been discussed as an alternative. However, the literature concerning shunt operations is controversial with significant morbidity and mortality reported. Tsimaratos *et al.* reported two pediatric cases of splenorenal shunt before KTx, with the death of both patients because of encephalopathy. A recent review analyzed 1230 patients of all ages [15] and reported an improvement in 25 of 34 patients. However, the authors stated that there were few data on shunt morbidity. Thus, in our center we opted to use CLKT for patients with portal hypertension, especially as kidney transplantation was inevitable. However, it must be admitted that the optimal procedure (portosystemic shunt vs. CLKT) has not been evaluated in a systematic manner. Clearly, the ideal setting for this approach – a randomized trial – is ethically problematic. Registry data including all patients with both procedures are not currently available and would be helpful. Recommendations based on our experience are summarized in Table 4.

Outcomes

Our series is highly selective, as patients were referred from other German centers for evaluation of CLKT. Nevertheless, we are convinced that the strategy of a combined transplantation is appropriate for these children despite the surgical challenge.

We achieved a patient survival rate of 100% after CLKT with our approach, which is excellent by comparison with survival rates of 70–80% in recently published studies of patients undergoing transplantation procedures for ARPKD [9, 22]. Organ survival rates are significantly lower in our series because of the fact that one patient had to undergo retransplantation twice.

The median age of our cohort at transplantation was 10 years and it included only two patients less than 5 years of age. However, our own data from patients suffering from primary hyperoxaluria showed that combined transplantation can be carried out safely for patients with body weights as low as 10 kg [16]. This is important because all patients had antenatal oligohydramnios, and early renal failure and liver disease may develop in addition to postnatal evidence of pulmonary hypoplasia.

Liver function was stable in all patients at the end of our study. In one patient (P7), a liver retransplantation had to be carried out because of chronic liver failure with ascites and hepatic vein stenosis. All other organs functioned well and showed normal liver synthesis. Despite multiple hospital stays and frequent follow-up visits, all patients attended a regular school.

Table 3. Scoring of identified *PKHD1* mutations for likely pathogenicity with different bioinformatic tools.

Patient	*PKHD1* mutation	MutationTaster*	PolyPhen2†	PMut‡	AlignGVGD§
P2	c.4220T>G (p.Leu1407Arg)	Disease-causing	Probably damaging	Pathological	Highly likely pathogenic
	c.10174C>T (p.Gln3392X)	Disease-causing	Nonsense mutation	Nonsense mutation	Nonsense mutation
P3	c.107C>T (p.Thr36Met)	Neutral	Probably damaging	Pathological	Highly likely pathogenic
	c.8581A>G (p.Ser2861Gly)	Neutral	Benign	Pathological	Highly likely pathogenic
	c.8870T>C (p.Ile2957Thr)	Indeterminate	Probably damaging	Pathological	Highly likely pathogenic
P4	c.664A>G (p.Ile222Val)	Neutral	Benign	Neutral	Indeterminate
	c.2542T>A (p.Trp848Arg)	Neutral	Probably damaging	Pathological	Highly likely pathogenic
P5	c.107C>T (p.Thr36Met)	Neutral	Probably damaging	Pathological	Highly likely pathogenic
P6	c.107C>T (p.Thr36Met)	Neutral	Probably damaging	Pathological	Highly likely pathogenic
	c.9239G>A (p.Gly3080Glu)	Indeterminate	Probably damaging	Pathological	Highly likely pathogenic
P7	c.602+5G>T (IVS8+5G>T)	Canonical splice defect	Cannonical splice defect	Canonical splice defect	Canonical splice defect
	c.602+5G>T (IVS8 + 5G>T)	Canonical splice defect	Canonical splice defect	Canonical splice defect	Canonical splice defect
P8	c.7062delA (p.Ala2355LeufsX60)	Disease-causing	Frameshift mutation	Frameshift mutation	Frameshift mutation
	c.8642+1G>T (IVS55+1G>T)	Canonical splice defect	Canonical splice defect	Canonical splice defect	Canonical splice defect

*Mutation Taster (http://www.mutationtaster.org) (Schwarz JM *et al.* MutationTaster evaluates disease-causing potential of sequence alterations. *Nat Methods* 7: 575–6, 2010).
†PolyPhen 2 (Polymorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2/index.shtml).
‡PMut (http://mmb.pcb.ub.es/PMut/)
§AlignGVGD (http://agvgd.iarc.fr/index.php): multiple sequence alignment of orthologs.

Table 4. Summary of recommendations: Hamburg experience in children with ARPKD with various degree of the disease.

	Kidney		
Liver	Normal kidney function/ CKD I	CKD II-III	CKD IV/ ESRD
Congenital hepatic fibrosis, no portal hypertension, normale platelet count, normal liver synthesis	Follow-up	Follow-up	KTx Frequent Doppler-ultrasound liver/spleen
Portal hypertension, fibrosis II-III, no varices	Follow-up, Frequent Doppler-ultrasound liver/spleen	Follow-up, Frequent Doppler-ultrasound liver/spleen	KTx Cave: cholangitis, sepsis Liver biopsy before KTx, Frequent Doppler-ultrasound liver/spleen
Portal hypertension, fibrosis IV-cirrhosis, varices ± bleeding	LTx Porto-systemic shunt	LTx, If applicable: Kidney after Liver (KALT)	CLKT

CKD, chronic kidney disease; CLKT, combined liver and kidney transplantation; ESRD, end-stage renal disease; KTx, kidney transplantation; LTx, liver transplantation.

The longitudinal growth of our cohort demonstrates the possibility of catch-up growth after CLKT. Statistical analysis showed significantly better growth after CLKT for ARPKD. These results should be kept in mind when the decision for CLKT has to be made and when parents and patients need to be advised. However, our data do not allow us to compare growth after CLKT with growth after single kidney transplantation in patients with ARPKD.

In summary, an indication for CLKT in patients with distinct clinical symptoms such as ESRD and severe portal hypertension with bleeding varices can be made despite the lack of controlled data. In borderline cases, the clinical hepatic phenotype together with laboratory data, longitudinal Doppler ultrasound examinations and liver biopsies are important parameters that can help to decide whether CLKT is a preferable option.

Using this approach, our single-center experience showed favorable long-term outcomes without mortality after a median follow-up of 4.6 years, and confirmed that CLKT is an important treatment option for children with ARPKD. As suggested by Srinath and Shneider [15], an interdisciplinary team of experienced pediatric nephrologists, pediatric hepatologists, and pediatric radiologists is important for the care of these patients.

Authorship

FB: design of study, data collection, data analysis, statistical analysis, histological analysis, writing of the manuscript, approval of final manuscript as submitted. AL: data collection, data analysis, writing of the manuscript, approval of final manuscript as submitted. CM: data collection, approval of final manuscript as submitted. KH: data collection, ultrasound examinations, analysis of ultrasound results, approval of final manuscript as submitted. HS: histological analysis, approval of final manuscript as submitted. LF: writing of manuscript, approval of final manuscript as submitted. BN: writing of manuscript, approval of final manuscript as submitted. CB: genetic analysis, writing of manuscript, approval of final manuscript as submitted. RG: design of study, writing of manuscript, approval of final manuscript as submitted. MJK: design of the study, data collection, data analysis, writing of manuscript, approval of final manuscript as submitted.

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