Clinical manifestations of autosomal recessive polycystic kidney disease

Peter F. Hoyer

Purpose of review
To describe the recent increase in the understanding of the clinical manifestation of autosomal recessive polycystic kidney disease (ARPKD), which is caused by mutations in the *PKHD1* gene. The change in nomenclature reflects the genetic contribution to the understanding of pleiotropic disease manifestations. The term 'hepatorenal fibrocystic disorder' or 'ARPKD–congenital hepatic fibrosis (CHF)' addresses the major organ manifestations of the disease.

Recent findings
More than 300 different mutations in the *PKHD1* gene have been described; however, there is no genotype–phenotype correlation. Cystic phenotype in the kidneys is highly variable. Renal oligohydramnios before 28 weeks of gestation may be lethal, whereas perinatal manifestations have a better prognosis. More than 60% of neonates with pulmonary hypoplasia may survive; about 25% need postnatal dialysis. After 10 years, 60% require renal replacement therapy. Liver fibrosis is always found and cholangiodysplasia is common. The Caroli phenotype is seen in up to 80% with perinatal manifestation. Recurrent cholangitis and cirrhosis may require liver transplantation in about 10% of patients. Neurocognitive development is in the usual range of children with moderate renal failure, but deserves further research.

Summary
The pleiotropic manifestations of ARPKD–CHF require multidisciplinary efforts to anticipate organ complications and to improve a possible good prognosis.

Keywords
ARPKD, Caroli, congenital hepatic fibrosis, hepatorenal fibrocystic disease, pediatric transplantation *PKDH1* gene

INTRODUCTION

Historically, autosomal recessive polycystic kidney disease (ARPKD) has undergone different medical descriptions; the terminology has changed from the Potter classification to 'hepatorenal fibrocystic disease'. Decades ago when no real treatment could be offered, major emphasis was put on the pathoanatomical descriptions of thin kidney sections. According to the size and cyst distribution, the Potter classification was developed. In adult nephrology, the term 'polycystic kidney degeneration' was used, because it was believed that the disease was degenerative in nature. Congenital and infantile manifestations of polycystic kidney disease (PKD) were named the infantile type of PKD, and later manifestations were designated the adult type. The focus on the inheritance of the disorders introduced the now broadly accepted terms autosomal dominant and autosomal recessive PKD. Molecular genetic discoveries and progress in medical treatment, including renal and liver replacement therapy, in young infants has broadened our understanding of ARPKD as a disease with great phenotypic variation, in relation to age as well as the severity of organ involvement. The term 'ARPKD' reflects kidney involvement as a major factor causing morbidity and early death, but neglects the importance of liver involvement. More appropriate descriptive terms are ARPKD–congenital hepatic fibrosis (CHF) or hepatorenal fibrocystic disease.

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KEY POINTS

- Autosomal recessive polycystic kidney disease (ARPKD), formerly described by the renal phenotype and recessive mode of inheritance, is now being ascribed to the underlying gene mutations in the *PKHD1* gene.
- Over 300 mutations have been described in over 86 exons expanding the *PKHD1* gene and have improved the description of the spectrum of organ-specific and clinical manifestations, but no genotype–phenotype correlations can be defined.
- Prenatal manifestations endanger survival through lung hypoplasia, early renal failure and early liver disease with cholangitis and portal hypertension.
- At the age of 10 years, 60% of patients require renal replacement or kidney transplantation, whereas about 10% may need liver transplantation, mainly sequential liver–kidney transplantation, with favorable results.
- Knowledge of the broad spectrum of clinical manifestations with pleiotropic effects in various organs should foster collaborative care and is essential for assessing the efficacy of future therapies.

The purpose of this review is to describe the recent increase in the understanding of the clinical manifestation of ARPKD–CHF, which is caused by mutations in the *PKHD1* gene.

ATTEMPTS TO CORRELATE GENOTYPE WITH PHENOTYPE HAVE SO FAR FAILED

ARPKD–CHF is by definition a rare disease affecting 1 out of 20 000 newborns; the carrier rate of the recessive gene is estimated to be 1 out of 70 [1]. The mutated gene located on chromosome 6p21.1–p12 is called *PKHD1*. It consists of 469 kilo base pairs and contains 86 exons. The gene product is an integral membrane protein with 4074 amino acids expressed on the renal tubular cells and biliary epithelial cells. It is named fibrocystin or polyductin and has been localized to primary ciliary bodies; however, the concise function of the protein remains unclear.

More than 300 mutations have been reported in the *PKHD1* gene [2,3▪▪], but attempts to find genotype–phenotype correlations, although attractive, have failed thus far. In most cases, two heterogeneous mutations cause the disease. Two truncating mutations may cause a more severe phenotype. A further discussion of the genetics in ARPKD is beyond the scope of this article.

CLINICAL PHENOTYPES VARY BY ONSET AND ORGAN INVOLVEMENT

Clinical manifestations of ARPKD–CHF can be classified by the onset of symptoms and severity or by the type of organ involvement. Prenatal renal manifestations are usually followed by a bad course with oligohydramnios and respiratory failure early after delivery, whereas manifestations later than 1 month of age have a longer renal survival. Almost all patients have liver fibrosis, but clinical manifestations are highly variable. Blyth and Ockenden [4] described cases with a reciprocal relationship between renal and liver involvement, and they classified an infantile and adult phenotype. A group of patients had congenital liver fibrosis and developed renal cysts later in life, whereas others had predominantly kidney involvement and developed visible liver fibrosis much later. These excellent historical observations were of course lacking a molecular genetic analysis. Better perinatal survival and organ replacement therapies, together with genetic testing and discrimination from other cystic kidney diseases, allow us to describe a broader spectrum of ARPKD–CHF with underlying mutations in the *PKHD1* gene. In the last 2 years, some authors have focused on the spectrum of clinical manifestations [3▪▪,5▪,6▪▪].

IMAGING AND RENAL PATTERN OF AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE–CONGENITAL HEPATIC FIBROSIS

According to Turkbey *et al.* [7], renal cyst expression can be classified into four major patterns: partial medullary involvement, complete medullary involvement but preserved cortex, complete medullary involvement with less than 50% cortical involvement, and the most severe form with complete medullary and more than 50% cortical involvement (Fig. 1).

The question arises whether this can be used for the diagnosis of ARPKD–CHF.

In a recent systematic overview, Liebau and Serra [9] concentrated on the value of MRI in PKD, especially on kidney volume. The rationale for this is the availability of treatment options, which theoretically should inhibit cyst growth. In this context, the measurement of total kidney volume should be a marker for the efficacy of therapy in clinical trials. Although several studies in adult patients with autosomal dominant polycystic kidney disease (ADPKD) have addressed this clinical marker with MRI, there are no comparable data in a pediatric cohort with ARPKD–CHF. Liebau and Serra summarized from the literature that with disease progression, ARPKD kidneys tend to shrink in parallel with the decline of renal function. In a group of 31 pediatric patients, there is a weak negative correlation between total kidney volume and kidney function; however, there was a great

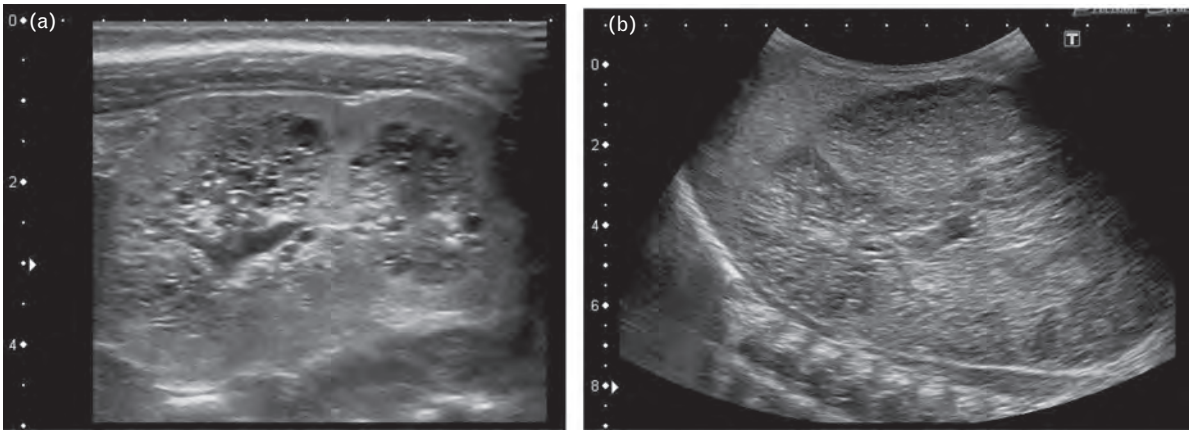

FIGURE 1. Ultrasound pictures of ARPKD kidneys with various cyst distribution, predominantly in the medulla (a) and diffuse corticomedullary distribution (b). ARPKD, autosomal recessive polycystic kidney disease. Reproduced with permission [8].

scattering of data, including patients with up to 1500 ml total kidney volume. High-resolution ultrasound seems to be more sensitive in the detection of small cortical cysts than MRI.

Liebau pointed out that localization of the cysts within the kidney might help clinicians to differentiate between ADPKD, ARPKD and nephronophthisis. Importantly, there are no data that the diagnosis of ARPKD can be made by renal imaging alone. There may be a considerable overlap in phenotypes obtained by imaging.

In a study from the National Institute of Health (NIH) study [5▪], 90 patients were referred to the NIH by pediatric nephrologists or gastroenterologists. In 73 patients, the diagnosis was confirmed by the mutational analysis with at least one *PKHD1* mutation. In 74% of patients, the initial symptoms were kidney related. On ultrasound, 37% had only medullary cysts and in 63% cysts showed a corticomedullary distribution. In patients younger than 5 years, only 22% had medullary cysts and the vast majority had corticomedullary cysts. In the older patients, the distribution pattern was almost equal, 45 versus 55%. Not surprisingly, the mean GFR was lower in the younger group: 66 ml/min/1.73 m^2 versus 85 and 79 ml/min/1.73 m^2 in the older group.

PERINATAL DIAGNOSIS IS A RISK FACTOR FOR EARLY RENAL FAILURE AND DEATH

It is well known that prenatal diagnosis with oligohydramnios may lead to a fatal outcome. However, systematic longitudinal data are scarcely available. Many obstetricians advice abortions and still call it Potters' syndrome or Potter kidneys. The true numbers are not known. Two recent studies, one from Helsinki, Finland [6▪▪] and one from Birmingham, UK [10▪], provide data on the outcome and time of end stage renal disease (ESRD). The Finish cohort included 33 patients with a median follow-up of 10.6 years. In 15 patients (45%), the diagnosis was made prenatally, whereas in others, the diagnosis was made at a median of 2.7 days after birth (range 0–13 years). Sixteen patients had pulmonary hypoplasia and needed mechanical ventilation. Six of these patients died during the neonatal period. A total of 27 patients survived the neonatal period and 12 of them belonged to the group diagnosed before birth. Five newborns needed dialysis in the first week of life. Their kidneys were so large that bilateral nephrectomy was performed before dialysis could start (Fig. 2). This means about 20% who survived after birth need immediate dialysis! Overall, 20 children developed ESRD. Renal survival calculated by the Kaplan–Meier method was 62% at 1 year, 50% at 5 years and 38% at 10 years. It can be concluded from this study that survival is possible despite prenatal diagnosis and the need for renal replacement during the first weeks of life. The severity of pulmonary hypoplasia may limit postnatal life; in this study, 6 out of 16 with pulmonary hypoplasia died.

The Birmingham study focused primarily on the cases with early liver involvement. It is of note that those presenting with symptoms in the neonatal period developed ESRD at a median age of 6 years, whereas those requiring ventilation developed ESRD before the age of 5 years.

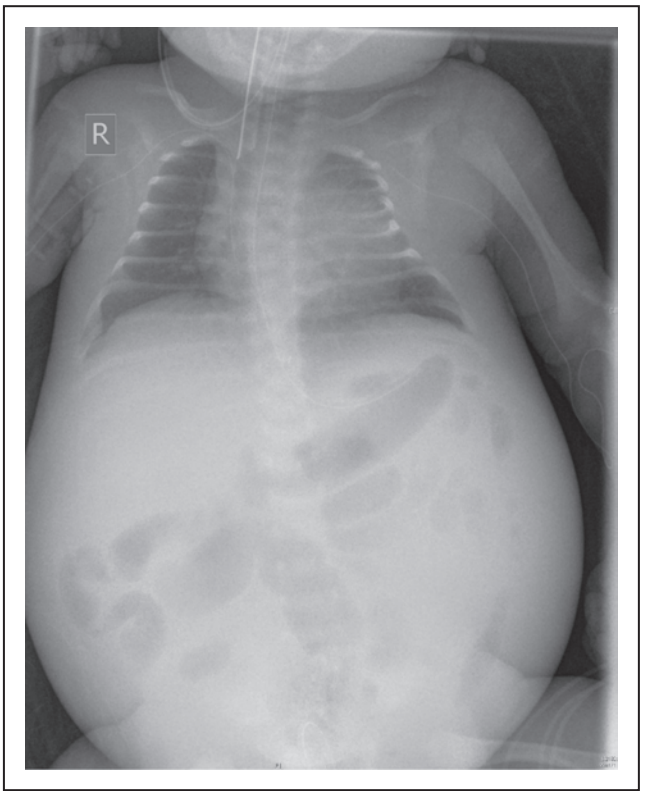

FIGURE 2. Newborn with pulmonary hypoplasia requiring ventilation. No renal function. The abdomen is massively enlarged. Before peritoneal dialysis was initiated, the kidneys have to be removed. Reproduced with permission [8].

PULMONARY MANIFESTATIONS MAY BE LETHAL IN SOME BUT NOT ALL PATIENTS

As described above, children with severe pulmonary hypoplasia may die in the perinatal period; however, more positively, as reported in the Finish cohort, the majority survived.

Respiratory failure after birth may be for two reasons: one is thought to be a consequence of renal oligohydramnios (ROH) and the other factor may be massive enlargement of the kidneys, compromising the diaphragm motility, or leading to compression of the intrathoracic space.

Many obstetricians believe that intra-amniotic fluid filling may improve lung function. However, there are no prospective studies to demonstrate a measureable effect in patients with the prenatal diagnosis of ARPKD. One single-center study [11] on ROH highlighted that the lung prognosis may depend on the time of first diagnosis of ROH. An onset after 28 gestational weeks may have a better prognosis. This observation should be considered before a postnatal lethal course is predicted.

Diaphragm and lung compression are very serious complications. Rapid postnatal kidney growth may lead to abdominal compartment syndrome. The Finish group reported that in some patients the kidneys must be removed. We have made the same observations. Massive growing kidneys jeopardize ventilation and make nutrition or peritoneal dialysis impossible [12].

RENAL PHENOTYPE-ASSOCIATED MANIFESTATIONS ARE ARTERIAL HYPERTENSION, HYPONATREMIA AND URINARY TRACT INFECTIONS

Almost all patients with early renal manifestations suffer from severe arterial hypertension [12], and some very young infants require up to five antihypertensive drugs to control their blood pressure (BP). With increasing age, BP problems become less severe and BP is easier to manage. It is of note that patients with an early manifestation or ADPKD have much less, or no, BP problems. Hyponatremia is frequently observed in infants with early renal phenotype. Several studies stress a major role of the renin–angiotensin–aldosterone system and vasopressin.

It is of note that urinary tract infections are reported at rates of 20–50% in patients with ARPKD, with girls having a higher frequency of urinary tract infections than boys.

MAJOR HEPATIC MANIFESTATIONS, CONGENITAL HEPATIC FIBROSIS AND CAROLI SYNDROME PROGRESS WITH TIME

Nephrologists looking just at the kidneys may overlook the development of hepatic manifestations. Patients predominantly expressing the hepatic phenotype are often first seen by a pediatric gastroenterologist, who may miss the renal manifestations if not severe or if the renal manifestations develop later in life. The liver manifestations include CHF and cholangiodysplastic changes, which have their origin in duct plate malformations with abnormal branching, bile duct dilatation and fibrosis. Defective signaling of primary cilia on bile duct epithelial cells is thought be a causative factor. Depending on the degree of fibrosis and ductal plate malformation, the liver phenotype may vary in severity. Some patients have noncirrhotic liver fibrosis or CHF with cholangiodysplasia, and others the Caroli type with massive intrahepatic bile duct dilation (Fig. 3). The latter is called Caroli syndrome. Modern gene analysis has demonstrated that Caroli syndrome also has mutations in the *PKHD1* gene, so that it belongs to the ARPKD disease complex.

CHF is histologically almost always present in ARPKD, although it may be clinically undetectable in infants. It progresses with time and may lead to

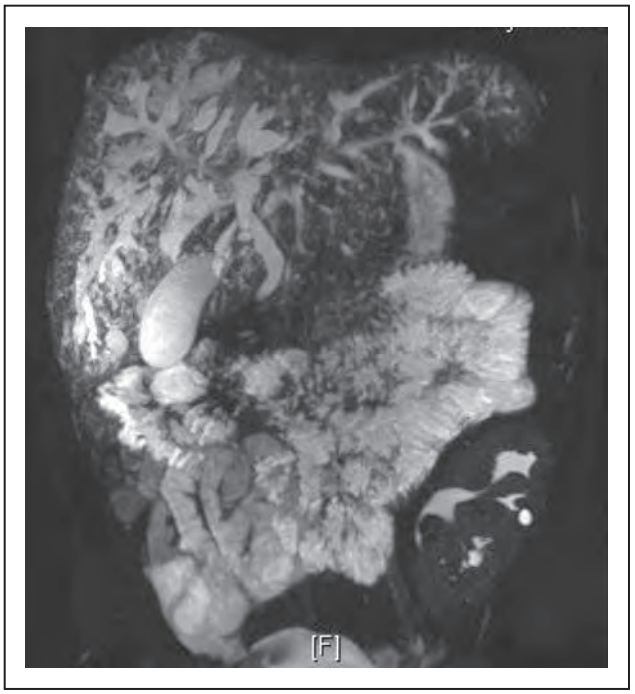

FIGURE 3. MRI of ARPKD–CHF with Caroli syndrome. Fusiform dilations of the intrahepatic biliary ducts. ARPKD, autosomal recessive polycystic kidney disease; CHF, congenital hepatic fibrosis. Reproduced with permission [8].

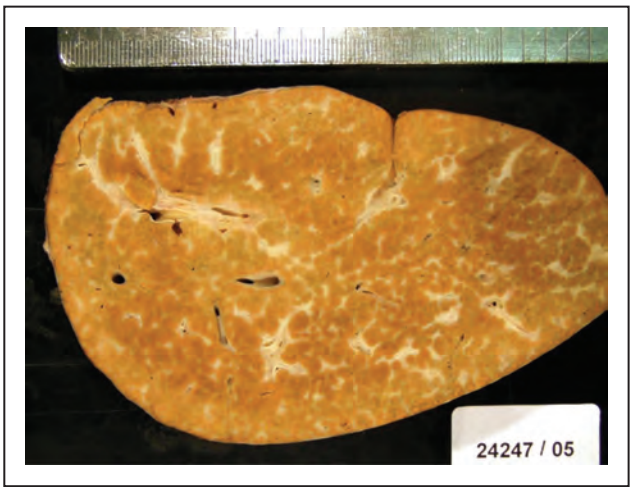

FIGURE 4. Severe liver fibrosis in ARPKD–CHF; liver after hepatectomy because of liver transplantation. ARPKD, autosomal recessive polycystic kidney disease; CHF, congenital hepatic fibrosis. Reproduced with permission [8].

severe portal hypertension. Usually, liver enzymes remain within the normal range. Liver synthetic function is usually not impaired but has been seen in severe cases of liver disease.

This means that a normal liver ultrasound and normal biochemical parameters do not exclude CHF. With disease progression, the echogenicity of the liver may increase, and periportal fibrosis can result in portal hypertension with an increase in spleen size. In advanced stage of fibrosis (Fig. 4), collaterals and porto-systemic shunts may develop including esophageal varices, which can lead to gastrointestinal bleeding.

Cholangiodysplastic changes may be invisible unless irregular bile ducts can be seen on ultrasound or cholangio-MRI. Some patients have discrete localized cholangiocystic features, which slowly progress over time. The Caroli phenotype shows marked cystic bile duct dilations, which may affect the whole liver or predominantly one lobe. Secondary bile casts and calcifications may lead to a mixed pattern with cysts and high echogenic areas. Patients with cholangiodysplastic changes are at risk to develop cholangitis. In case of unexplained fever an increase of biochemical parameter indicating cholestasis should enable the diagnosis. Jaundice is not obligatory, but elevated bile acids and gamma-glutamyltransferase are sensitive parameters. Some recent publications focus on the presentation and clinical consequences of hepatic manifestations. In the Finish study mentioned above [6▪▪], 13 (48%) out of 27 patients who survived the neonatal period developed clinical portal hypertension at a median age of 5 years. A total of 16 patients underwent 1–19 gastroscopies. Eight patients suffered from upper gastrointestinal tract bleeding; all of the patients were treated by sclerotherapy and one patient received a splenorenal shunt. Ascites was seen in five patients.

Dilation of the biliary tract was diagnosed in 9 (33%) patients at a median age of 3 years. Chronic renal failure diagnosed in the first year of life was a clear risk factor for biliary abnormalities (60 versus 18%). Three of these nine patients had the Caroli phenotype. Twenty patients underwent liver biopsies; all showed liver fibrosis, four bile duct changes and one a hepatoblastoma. Kaplan–Meier estimates for survival without liver symptoms were 100% at 1 year, 72% at 2 years and 42% at 10 years.

The Birmingham study [10▪] analyzed 40 patients with CHF and in 32 the diagnosis of ARPKD was established by mutations in the *PKHD1* gene. The remaining patients had other cystic kidney diseases. Patients were compared according to a Caroli phenotype versus CHF phenotype. Early perinatal–neonatal presentation was more likely to have Caroli syndrome (78%) versus CHF (22%).

Later presentation was more likely to be associated with CHF (62%) versus Caroli syndrome (38%). Clinical parameters such as low platelets or bleeding varices did not differ, whereas cholangitis and early chronic renal failure were more frequent in patients with the Caroli phenotype. They conclude, from a

more gastroenterological point of view, that disease presentation in the neonatal period is more likely to have complicated phenotypes with Caroli syndrome, cholangitis and chronic renal failure.

The NIH study mentioned above was dependent on referral and included more adult patients. Neonatal patients were not reported separately and the age range was from 1 to 56 years. The Caroli phenotype was noted in about 72% in all age groups.

Splenomegaly tended to increase from 60 to 70% with older age, whereas platelet count as a marker for portal-hypertension-associated splenomegaly decreased with age. The study concluded that platelet count is the best predictor of the severity of portal hypertension. About 70% of patients had biliary abnormalities and liver and kidney disease are independent in severity. However, it must be emphasized that this interpretation might hold true for patients beyond the first year of life.

PANCREAS MAY BE INVOLVED IN RARE CASES

There are no systematic investigations of pancreatic manifestations in ARPKD. As intact primary cilia function may be involved in pancreas development, pathological changes might not be a surprise. Occasional observations describe cystic duct dilatation. We observed a boy after combined liver kidney transplantation who developed pancreatic cysts after 3 years. In some patients, dystopic pancreas islets were found in the liver after hepatectomy for liver transplantation (J. Becker, personal communication). No data exist about diabetes mellitus. In some cases, recurrent episodes of cholangitis with biliary concrement formation may damage the pancreas.

NEUROCOGNITIVE FUNCTION IS IMPAIRED IN AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Neurocognitive dysfunction in ARPKD has been, for first time, very recently studied [13▪▪].

Twenty-three patients with ARPKD, mean 7.5 years, were compared with matched controls with impaired kidney function. In both groups, a larger proportion of children scores in all tested domains were below 1 standard deviation score (SDS) of normal, which is interpreted as at risk for neurocognitive dysfunction. This study did not find disease-specific neurocognitive deficits. However, this study is limited to mild-to-moderate chronic kidney disease (CKD). Further studies with more ARPKD-related comorbidities, that is, advanced liver disease, are needed to define the consequences of more severe forms of ARPKD.

TERMINAL ORGAN FAILURE AND ORGAN REPLACEMENT THERAPY

A general improvement in therapy has improved the short-term and medium-term survival. However, with increasing age, more children will need renal replacement therapy. As described above, renal survival at 10 years is only 38%.

Recent data from the U.S. scientific Registry of transplant recipients [14▪] analyzed the data from 1990 to 2010. A total of 716 pediatric patients with PKD were registered. Kidney transplants (KTx) were performed in 602 patients at a median age of 9.9 years, liver transplants (LTx) in 73, median age 8.7 years, and sequential liver–kidney transplantations (SLKTx) in 41, median age 9.2 years. In this cohort, the reason for liver replacement was Caroli syndrome in 29% and CHF in 71%. Mortality after LTx was 23%, after KTx 10% and after SLKTx 12%. It is of note that the overall mortality has improved in the recent decade.

Telega *et al.* [15] reviewed dual kidney–liver transplantation in ARPKD. Whereas survival after KTx in ARPKD is in the order of other underlying kidney diseases, the mortality after KTx is in 60–80% related to ascending cholangitis. The immunosuppression after KTx may increase the risk for cholangitis. Therefore, SLKTx should be considered for patients with ESRD and liver disease, especially with Caroli syndrome or a history with cholangitis.

A recent report from Hamburg [16] as well as our own center's experience show excellent survival rates after SLKTx, justifying this strategy in a subgroup at risk.

CONCLUSION

Without genetic mutational analysis, many cystic kidney diseases may be misclassified. The technical advances in detecting mutations in the *PKHD1* gene have improved the description of the spectrum of organ-specific and clinical manifestations in ARPKD. Systematic descriptions allow better risk adjustment, comprehensive care and diagnosis, foster collaborative care and better planning of organ replacement strategies.

With the understanding of the molecular basis of the pathophysiology, we hope that better targeted therapies can be developed as has been piloted in ADPKD. In future prospective therapies, knowledge of the broad clinical manifestations is of great importance to document the therapeutic effects.

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Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Gunay-Aygun M, Tuchman M, Font-Montgomery E, *et al.* PKHD1 sequence variations in 78 children and adults with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis. Mol Genet Metab 2010; 99:160–173.
2. Gunay-Aygun M, Font-Montgomery E, Lukose L, *et al.* Correlation of kidney function, volume and imaging findings, and PKHD1 mutations in 73 patients with autosomal recessive polycystic kidney disease. Clin J Am Soc Nephrol 2010; 5:972–984.
3. ■■ Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. Pediatrics 2014; 134:e833–e845.

An excellent comprehensive overview of pleiotropic effects, genetic testing, parent counseling and future therapeutic targets.

4. Blyth H, Ockenden BG. Polycystic disease of kidneys and liver presenting in childhood. J Med Genet 1971; 8:257–284.
5. ■ Gunay-Aygun M, Font-Montgomery E, Lukose L, *et al.* Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. Gastroenterology 2013; 144:112.e2–121.e2.

A description of 73 patients referred to the NIH and enrolled in a protocol focusing on the characteristics and clinical presentation of congenital hepatic fibrosis and biliary abnormalities.

6. ■■ Luoto TT, Pakarinen MP, Jahnukainen T, Jalanko H. Liver disease in autosomal recessive polycystic kidney disease: clinical characteristics and management in relation to renal failure. J Pediatr Gastroenterol Nutr 2014; 59:190–196.

Finish data on the renal and hepatic manifestations of ARPKD–CHF, focussing on perinatal mortality and important data on long-term survival without ESRD and biliary disease.

7. Turkbey B, Ocak I, Daryanani K, *et al.* Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis (ARPKD/CHF). Pediatr Radiol 2009; 39:100–111.
8. Deeg K-H, Hofmann V, Hoyer PF, editors. Ultrasound diagnosis in pediatrics and pediatric surgery, 4th ed. Georg Thieme Verlag; 2014 [in German].
9. Liebau MC, Serra AL. Looking at the (w)hole: magnet resonance imaging in polycystic kidney disease. Pediatr Nephrol 2013; 28:1771–1783.
10. ■ Rawat D, Kelly DA, Milford DV, *et al.* Phenotypic variation and long-term outcome in children with congenital hepatic fibrosis. J Pediatr Gastroenterol Nutr 2013; 57:161–166.

A single-center report on 40 children with congenital hepatic fibrosis, describing the clinical presentation and course of hepatic fibrosis versus Caroli syndrome and survival without transplant.

11. Mehler K, Beck BB, Kaul I, *et al.* Respiratory and general outcome in neonates with renal oligohydramnios – a single-centre experience. Nephrol Dial Transplant 2011; 26:3514–3522.
12. Büscher R, Büscher AK, Weber S, *et al.* Clinical manifestations of autosomal recessive polycystic kidney disease (ARPKD): kidney-related and nonkidney-related phenotypes. Pediatr Nephrol 2014; 29:1915–1925.
13. ■■ Hartung EA, Matheson M, Lande MB, *et al.* Neurocognition in children with autosomal recessive polycystic kidney disease in the CKiD cohort study. Pediatr Nephrol 2014; 29:1957–1965.

A case–control study showing that children with ARPKD and mild-to-moderate CKD have impaired neurocognitive development to the same degree as children with other causes of CKD; however, more severe forms deserve further investigation.

14. ■ Wen JW, Furth SL, Ruebner RL. Kidney and liver transplantation in children with fibrocystic liver–kidney disease: data from the U.S. Scientific Registry of Transplant Recipients: Pediatr Transplant 2014; 18:726–732.

Recommended reading showing U.S. registry data on 716 pediatric patients with ARPKD–CHF who received a liver or kidney transplant or sequential liver kidney transplant. The favorable results are of great importance for counseling once a child is born with ARPKD–CHF.

15. Telega G, Cronin D, Avner ED. New approaches to the autosomal recessive polycystic kidney disease patient with dual kidney–liver complications. Pediatr Transplant 2013; 17:328–335.
16. Brinkert F, Lehnhardt A, Montoya C, *et al.* Combined liver–kidney transplantation for children with autosomal recessive polycystic kidney disease (ARPKD): indication and outcome. Transpl Int 2013; 26:640–650.