Autosomal Recessive Polycystic Kidney Disease: A Hepatorenal Fibrocystic Disorder With Pleiotropic Effects

abstract

Autosomal recessive polycystic kidney disease (ARPKD) is an important cause of chronic kidney disease in children. The care of ARPKD patients has traditionally been the realm of pediatric nephrologists; however, the disease has multisystem effects, and a comprehensive care strategy often requires a multidisciplinary team. Most notably, ARPKD patients have congenital hepatic fibrosis, which can lead to portal hypertension, requiring close follow-up by pediatric gastroenterologists. In severely affected infants, the diagnosis is often first suspected by obstetricians detecting enlarged, echogenic kidneys and oligohydramnios on prenatal ultrasounds. Neonatologists are central to the care of these infants, who may have respiratory compromise due to pulmonary hypoplasia and massively enlarged kidneys. Surgical considerations can include the possibility of nephrectomy to relieve mass effect, placement of dialysis access, and kidney and/or liver transplantation. Families of patients with ARPKD also face decisions regarding genetic testing of affected children, testing of asymptomatic siblings, or consideration of preimplantation genetic diagnosis for future pregnancies. They may therefore interface with genetic counselors, geneticists, and reproductive endocrinologists. Children with ARPKD may also be at risk for neurocognitive dysfunction and may require neuropsychological referral. The care of patients and families affected by ARPKD is therefore a multidisciplinary effort, and the general pediatrician can play a central role in this complex web of care. In this review, we outline the spectrum of clinical manifestations of ARPKD and review genetics of the disease, clinical and genetic diagnosis, perinatal management, management of organ-specific complications, and future directions for disease monitoring and potential therapies. Pediatrics 2014;134:e833–e845
Autosomal recessive polycystic kidney disease (ARPKD; MIM 263200) is an important inherited cause of chronic kidney disease (CKD), with an estimated incidence of 1 in 20 000 live births. The most typical disease expression occurs in neonates and includes a history of oligohydramnios, massively enlarged kidneys, and the "Potter" sequence with pulmonary hypoplasia that leads to respiratory insufficiency and perinatal death in ~30% of affected newborns.

Improved survival of infants resulting from advances in neonatal supportive care over recent decades has allowed recognition of a broader spectrum of disease manifestations. In addition, identification of the causative gene, PKHD1, has allowed clinicians to recognize that patients with disparate phenotypes all have defects in the same disease gene.

The typical renal phenotype of ARPKD consists of enlarged, echogenic kidneys with fusiform dilatation of the collecting ducts. Patients can progress to end-stage renal disease (ESRD) at varying ages. ARPKD also has important effects on other organ systems. Notably, patients have liver disease consisting of dilated biliary ducts, congenital hepatic fibrosis, and portal hypertension (Caroli syndrome). Systemic hypertension is prevalent and can be severe.

Children with ARPKD may also be at risk for neurocognitive dysfunction. Families of children with ARPKD also face a number of challenges. As genetic testing technology has advanced, not only do families face decisions regarding testing of a symptomatic child, they must also confront issues such as testing of asymptomatic children and consideration of new reproductive technologies such as preimplantation genetic diagnosis (PGD). Many families will be confronted with decisions regarding dialysis and/or transplantation, kidney, liver, or sometimes both. It is essential that providers caring for these patients be well versed not only in the biology of the disease but also in its psychosocial implications.

In this article, we review the genetic basis of ARPKD, clinical and genetic diagnosis, perinatal management, management of organ-specific and systemic complications, and considerations of dialysis and transplantation and explore future directions for monitoring disease progression and potential therapies.

**GENETICS OF ARPKD**

**Background of the Gene and Protein**

ARPKD is caused by mutations in PKHD1, a large ~500-kb gene with a complex splicing pattern located on chromosome 6p21.1-p12.

The product of PKHD1, fibrocystin/polyductin (FPC), is a single-membrane spanning protein with multiple isoforms. It is expressed predominantly in the kidney (mostly in collecting ducts and thick ascending loops of Henle), liver (in bile duct epithelia), and pancreas. In renal tubular and biliary epithelial cells, FPC localizes to apical membranes, the primary cilia/basal body, and mitotic spindle.

The exact function of FPC remains unclear. However, numerous proteins associated with other hepatorenal fibrocystic diseases (Table 1) also localize to the primary cilia/basal body (Fig 1). This suggests a central role for the primary cilium in development and maintenance of renal tubular architecture and has led some to characterize these disorders collectively as "ciliopathies." Through its interactions with the autosomal dominant polycystic kidney disease (ADPKD) protein polycystin-2, FPC may form part of a common signaling pathway that also includes polycystin-1.

**Human Mutations**

ARPKD mutations have been identified along the entire length of the PKHD1 gene, and multiple mutation types have been described as pathogenic. To date, >300 pathogenic mutations have been cataloged in the ARPKD Mutation Database (http://www.humgen.rwth-aachen.de), of which approximately half are missense changes. The most common mutation overall is a missense mutation in exon 3, c.107C>T (p.Trp36Met), which accounts for ~20% of all mutated alleles. Aside from this mutation, which has been observed in a large number of unrelated patients, there do not appear to be any mutational hotspots. Indeed, a large proportion of mutations are unique to a single pedigree.

**Genotype-Phenotype Correlations**

Multiple studies have attempted to elucidate genotype-phenotype correlations in ARPKD. Given the diversity of PKHD1 mutations, most patients are compound heterozygotes, that is they carry 2 different mutant alleles. The functional effect of any particular mutant allele can therefore be difficult to discern.

Nevertheless, some broad themes have emerged from these studies. Notably, patients with 2 truncating mutations typically have a severe phenotype leading to perinatal demise. However, not all missense mutations lead to a more benign outcome; indeed, a number of missense mutations result in severe phenotypes when present with a truncating mutation or in homozygous form.

Numerous groups have attempted to categorize sequence variations based on likelihood of pathogenicity, many of which are cataloged in the ARPKD Mutation Database. However, because many patients will be found to have novel PKHD1 variants, interpretation of genetic testing results can be challenging.

Genetic modifiers likely also play a significant role in disease expression. This
is illustrated by the presence of significant phenotypic variability in a subset of families, for example, in a study of 126 unrelated families, 20 sibships showed widely discordant phenotypes (perinatal lethality in 1 sibling and survival into childhood in the other).6

**Genetic Testing**

Mapping of the ARPKD locus to chromosome 6p21.1-p1245 in the mid-1990s allowed the use of haplotype (linkage) analysis for genetic confirmation of the diagnosis, including prenatally,1 provided DNA from a previously affected child and the parents was available.

Identification of *PKHD1* has since allowed diagnosis by direct sequencing. In various cohort studies,5,10,11,14,34,35,37–50,42,43,48 mutation detection rates have ranged from 42% to 87% of tested alleles, and ~95% of patients could be found to have at least 1 *PKHD1* mutation. Generally, mutation detection rates are higher for patients with severe early-onset disease because they are more likely to have truncating mutations that are easier to detect.

A number of laboratories offer clinical genetic testing for ARPKD. These are summarized on the GeneTests Web site (www.genetests.org), and in the National Institutes of Health Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr). Most laboratories offer direct sequencing of the entire coding region, with expected mutation detection rates similar to recent studies of ~80%. However, direct sequencing cannot detect all mutations (e.g., those in noncoding exons or in promoter or regulatory regions). Some laboratories also offer multiplex ligation-dependent probe amplification to detect large deletions or genomic rearrangements.49 In families with >1 affected child, haplotype analysis remains a valuable tool when only 1 or no *PKHD1* mutations have been identified.50

Another challenge in establishing a molecular diagnosis is that several other diseases can mimic the clinical presentation of ARPKD. For example, patients with mutations in the ADPKD genes, *PKD1* and *PKD2*, can present with early-onset renal cystic disease indistinguishable from ARPKD.51–53 In some cases, this can occur in families with a mild phenotype in previous generations51; in others, ARPKD-like phenotypes have been described when 2 incompletely penetrant *PKD1/2* alleles are inherited in *trans*.52,53 when a *PKD1/2* mutation is inherited in *trans* with a mutation in another cystic kidney disease gene such as *HNF1β*.53 In addition, it must be noted that the most common cause of hyperechoic fetal kidneys is reported to be *HNF1β*-related.

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**Table 1 Hepatorenal Fibrocystic Diseases: Summary of Genetics and Clinical Features**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene(s)</th>
<th>Renal Disease</th>
<th>Hepatic Disease</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARPKD</td>
<td><em>PKHD1</em></td>
<td>Collecting duct dilatation</td>
<td>CHF, Caroli disease</td>
<td>Growth retardation</td>
</tr>
<tr>
<td>ADPKD</td>
<td><em>PKD1</em>, <em>PKD2</em></td>
<td>Cysts along entire nephron</td>
<td>Biliary cysts; CHF</td>
<td>Minimal in children</td>
</tr>
<tr>
<td>NPHP</td>
<td><em>NPHP1–NPHP15</em></td>
<td>Cysts at the corticomedullary junction</td>
<td>CHF</td>
<td>Tapetoretinal degeneration, situs inversus</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td><em>JBS1–JBS20</em></td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF, Caroli disease</td>
<td>Cerebellar vermis hypoplasia with episodic hyperpnea, abnormal eye movements, intellectual disability</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td><em>BBS1–BBS15</em></td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF</td>
<td>Retinal degeneration, obesity, postaxial polydactyly, hypogonadism in males, intellectual disability</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td><em>MKS1–MKS10</em></td>
<td>Cystic dysplasia</td>
<td>CHF (rare)</td>
<td>Occipital encephalocele, polydactyly</td>
</tr>
<tr>
<td>Oral-facial-digital syndrome, type I</td>
<td><em>ODF1</em></td>
<td>Glomerular cysts</td>
<td>CHF</td>
<td>Malformations of the face, oral cavity, and digits</td>
</tr>
<tr>
<td>Glomerulocystic disease</td>
<td><em>PKD1</em>, <em>TCF2</em>, <em>UMN0</em></td>
<td>Enlarged, normal or hypoplastic kidneys</td>
<td>CHF (with <em>PKD1</em> mutation)</td>
<td>Diabetes, hyperuricemia</td>
</tr>
<tr>
<td>Jeune syndrome (asphyxiating thoracic dysrophy)</td>
<td><em>IFT80 (ATD2)</em></td>
<td>Cystic dysplasia</td>
<td>CHF, Caroli disease</td>
<td>Short stature, skeletal dysplasia, small thorax, short limbs, polydactyly, hypoplastic pelvis</td>
</tr>
<tr>
<td>Renal-hepatic-pancreatic dysplasia (hermank II syndrome)</td>
<td><em>DYNC2H1 (ATD3)</em></td>
<td>Cystic dysplasia</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>Pancreatic cysts, dysplasia, and/or fibrosis; splenic abnormalities, situs inversus</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td><em>PEX1–3, 5–6, 10–11, 13, 14, 16, 19, 26</em></td>
<td>Renal cortical microcysts</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>Hypotonia, seizures, agenesis/hypoplasia of corpus calleous, characteristic facies, skeletal abnormalities, neonatal death</td>
</tr>
</tbody>
</table>

Adapted with permission from Somlo and Guay-Woodford.143 CHF, congenital hepatic fibrosis; NPHP, nephropathia.
A number of the other hepatorenal fibrocystic diseases listed in Table 1 can also have clinical manifestations that overlap with ARPKD. Thus, mutational analysis of PKHD1 using current single-gene testing methodologies should not be considered as a first-line diagnostic approach for infants and children presenting with an ARPKD-like phenotype. It is expensive and potentially confounded by the existence of phenocopy disorders. Moreover, the high frequency of missense mutations makes pathogenicity predictions for single nucleotide variants challenging, and particular caution is required when only novel or rare missense changes are detected. The one clear exception to this guidance is in the context of planned PGD in which putative PKHD1 mutations transmitted from the mother and father, respectively, must be prospectively identified.

Prenatal genetic testing can be performed by using haplotype analysis or PKHD1 sequencing as previously described. However, as discussed earlier, providing clear prognostic information based on sequencing results remains a challenge, although the presence of 2 truncating mutations is generally incompatible with survival, clinical consequences of other mutation types can be difficult to predict. Next-generation sequencing methods will likely also prove useful to differentiate ARPKD from other phenotypically similar entities.

PERINATAL CONSIDERATIONS

Prenatal Diagnosis of ARPKD

ARPKD is often first suspected based on routine prenatal ultrasound. Suggestive fetal features include symmetrically enlarged, echogenic kidneys (due to multiple microscopic cysts) with loss of corticomedullary differentiation due to medullary hyperechogenicity. Discrete cysts are sometimes observed. Oligohydramnios may be present due to poor fetal urine output. Many other hepatorenal fibrocystic diseases can have similar sonographic findings, however, so a definitive diagnosis is difficult based on imaging alone unless previous children have had a confirmed diagnosis of ARPKD. ADPKD can often be distinguished from ARPKD by the finding of increased corticomedullary differentiation in ADPKD (due to cortical hyperechogenicity with a relatively hypoechoic medulla). It is important to note, however, that normal sonographic findings do not exclude a diagnosis of ARPKD because abnormalities may not be seen until late in the second trimester (or beyond), even in infants who later manifest a severe phenotype at birth. In addition, the presence or absence of oligohydramnios does not always correlate with the degree of pulmonary insufficiency.

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a valuable alternative to prenatal diagnosis.\textsuperscript{62} To carry out PGD, the transmitted \textit{PKHD1} mutations must be prospectively identified. Then, a couple must undergo in vitro fertilization; the resulting embryo is biopsied, with removal of 1 or 2 blastomeres for genetic testing.\textsuperscript{63} Two groups have recently reported the birth of healthy infants after PGD in families at risk for ARPKD.\textsuperscript{62,64}

\textbf{Postnatal Management}

The estimated perinatal mortality rate in ARPKD patients is \textasciitilde 30\%, primarily due to respiratory compromise. One-year survival rates of 92\% to 95\%\textsuperscript{6,9} have been reported in patients who survive the first month of life. Although pulmonary hypoplasia is a major cause of respiratory compromise,\textsuperscript{65,66} an additional impediment is the presence of massively enlarged kidneys limiting diaphragmatic excursion. The enlarged kidneys may also interfere with nutrition due to gastrointestinal tract compression. The proportion of infants requiring mechanical ventilation is not well established; in one cohort, it was required in 41\% of neonates.\textsuperscript{9} Pneumothoraces also appear to be a relatively common complication.\textsuperscript{8,67}

Aggressive management strategies for infants with severe ARPKD have been described, including unilateral\textsuperscript{68–70} or bilateral\textsuperscript{67,71,72} nephrectomy to improve ventilation and nutrition. The optimal approach, however, is not well established given that the evidence base consists only of limited case reports and case series. Several of these reports have described improvements in nutrition after either unilateral\textsuperscript{68,69} or bilateral\textsuperscript{67} nephrectomy. Potential respiratory benefits of nephrectomy are less clear, particularly given the significant surgical risks in infants with severe respiratory compromise.\textsuperscript{70,72} Although some authors have reported successful weaning of respiratory support after nephrectomy,\textsuperscript{67,71,72} some infants with massively enlarged kidneys can be weaned from mechanical ventilation even without nephrectomy.\textsuperscript{68,69} In addition, morbidity associated with the earlier need for renal replacement therapy after nephrectomy must be carefully considered. Therefore, decisions surrounding possible nephrectomy for infants with severe ARPKD must be highly individualized.

Despite advances in neonatal supportive care including respiratory support and dialysis, the prognosis of infants with severe ARPKD is often uncertain. Parents and care providers may need to make difficult decisions surrounding possible limitation or withdrawal of care. Palliative care providers and/or medical ethicists can be invaluable in facilitating the decision-making process.

\textbf{RENAL MANIFESTATIONS}

Most ARPKD patients progress to ESRD, but the age at onset is highly variable. The overall renal survival rate in one large cohort of neonatal survivors was 86\% at age 5 years and decreased to 42\% by 20 years of age.\textsuperscript{6} However, age at ESRD onset appears to depend on age at initial presentation. In one cohort, 25\% of patients who presented in the perinatal period required renal replacement therapy by 11 years. In contrast, among those who presented after the perinatal period, the age at which 25\% of patients required renal replacement therapy was 32 years.\textsuperscript{44} Similarly, in another cohort, renal survival rate 20 years after diagnosis was 36\% in patients diagnosed before 1 year of age but was 80\% in those diagnosed at age 1 to 20 years.\textsuperscript{5}

Systemic hypertension is another important cause of morbidity in children with ARPKD, and its onset often precedes a decline in glomerular filtration rate.\textsuperscript{3,7} The prevalence of hypertension in various cohorts has been reported to range from 55\% to 75\%.\textsuperscript{2,3,7–9,73,74} Interestingly, some authors have noted that hypertension can sometimes normalize during the course of the disease.\textsuperscript{75,76}

The mechanism underlying hypertension in ARPKD is unclear. Some studies have suggested a low-renin mechanism,\textsuperscript{3,9} possibly due to dysregulation in sodium absorption in the structurally abnormal collecting ducts. However, other studies suggest a role for renin-angiotensin-aldosterone system (RAS) activation. A study in the \textit{PCK} rat model reported a significant increase in intrarenal, but not systemic, RAS activation.\textsuperscript{77} This finding may explain why previous studies did not detect increased plasma renin levels.\textsuperscript{3,78}

Hypertension in children with ARPKD is often severe enough to require multi-agent therapy.\textsuperscript{8,9} As in other causes of CKD, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are therapeutic mainstays and may be particularly helpful given data suggesting intrarenal RAS activation.\textsuperscript{77} However, there are no studies to determine whether therapy with these agents can slow disease progression in ARPKD. Strict blood pressure control has been shown to slow CKD progression in children with other diseases\textsuperscript{79}; thus it seems reasonable to also target blood pressures <90th percentile for children with ARPKD.

Hyponatremia has been reported to be common in early infancy; it was reported in 27\% of patients in one cohort\textsuperscript{9} and in 79\% of infants in another\textsuperscript{3} and may be due to an inability to maximally dilute the urine.\textsuperscript{5} However, other cohorts have reported much lower prevalences of hyponatremia.\textsuperscript{7,8}

Children with ARPKD appear to be at higher risk for urinary tract infections, possibly due to urinary stasis within the cystic, dilated collecting ducts. Urinary tract infections have been reported at rates of \textasciitilde 20\% to 50\% in various cohorts and are more common in girls.\textsuperscript{7–9,80}
Renal calcifications have also been reported to be common in older children with ARPKD\(^5,8^1\) and may be related to hypocitraturia and a defect in urine acidification due to renal failure.\(^8^1\)

**HEPATOBILIARY MANIFESTATIONS**

Patients with ARPKD invariably have a developmental biliary defect termed the ductal plate malformation.\(^8^2\) The abnormal intrahepatic bile ducts become progressively dilated and sometimes develop overt cysts. Progressive portal tract fibrosis can lead to portal hypertension and associated complications of hypersplenism and varices.\(^8^3\)

Although histologic biliary abnormalities are a universal feature, clinical expression varies widely. In 1 cohort, liver-related symptoms such as splenomegaly, cholangitis, or thrombocytopenia due to hypersplenism were presenting features in 26% of patients.\(^8^4\) Platelet counts were found to correlate well with spleen volume in this cohort.\(^8^4\) Liver transaminases are generally normal, and a fraction of patients have mild abnormalities in serum alkaline phosphatase, \(\gamma\)-glutamyltransferase, albumin, bilirubin, or prothrombin time.\(^7,8^4\)

In various cohorts, the proportion of ARPKD patients with imaging findings of liver disease has ranged from 45% to 90%.\(^2,7,8^4\) However, relatively fewer develop serious clinical complications of portal hypertension. Occurrence of bleeding esophageal varices and/or the need for portosystemic shunting has ranged from 10% to 40% of patients in various reports.\(^2,5,8,7,5,8^4\) Ascending cholangitis is another important complication and is a leading cause of morbidity and mortality in ARPKD patients particularly after kidney and/or liver transplantation.\(^8^5\)

In one cohort, about 7% of long-term survivors were reported to require liver transplantation, with primary indications being significant portal hypertension or recurrent cholangitis.\(^9\) The relationship between renal and hepatic disease severity in ARPKD is unclear. One study reported significant correlation between degree of renal dysfunction and portal hypertension.\(^8\) However, subsequent studies have documented no correlation between renal and hepatic disease severity.\(^9,7,5\) It appears that a subset of patients with ARPKD presenting later in life can have a liver-predominant phenotype with few or no manifestations of kidney disease.\(^5\)

**RADIOLOGIC DIAGNOSIS AND MONITORING**

Although renal ultrasound is sometimes used to monitor children with ARPKD, the prognostic value of imaging findings is unclear (Fig 2). Unlike in ADPKD, in which decline in renal function clearly correlates with increasing total kidney and cyst volume,\(^8^6,8^7\) there is no clear relationship between kidney size and function in ARPKD. There was no correlation between kidney length and serum creatinine in one large cohort.\(^7\) Another study found a weak inverse correlation between kidney function and volume in ARPKD patients, but there was marked variability.\(^4^4\) This study also found that patients with cysts limited to the renal medulla fared better than those with cortical and medullary abnormalities.\(^4^4\) It is unclear, however, if these findings represent different stages of disease progression or simply inherent differences in disease expression. Longitudinal studies of ARPKD have shown that kidney size trends to either remain stable or decrease over time.\(^7,8^8,9^1\)

Ultrasound can also be used to monitor sequelae of portal hypertension such as splenomegaly, presence of collateral vessels, and reversal of portal flow. However, these may be late findings in ARPKD and may not reflect underlying pathology such as progressive hepatic fibrosis.

MRI has been used for kidney and liver imaging in several studies,\(^4^4,8^4,9^2,9^3\); however, MRI has not come into routine clinical use because of the unclear prognostic significance of findings. Transient elastography (FibroScan) is a method of assessing liver fibrosis that has been validated in other disease processes and has been studied in children with ARPKD.\(^9^5\) However, additional studies are needed to assess the clinical utility of this technique in this patient cohort.

**DIALYSIS AND TRANSPLANTATION**

As discussed previously, some infants require dialysis in the newborn period after bilateral nephrectomy.\(^6^7,7^1,7^2\)

Given the technical challenges of hemodialysis in young infants, peritoneal dialysis (PD) is generally preferred. However, PD in infants with ARPKD can be complicated by peritoneal leak caused by peritoneal disruption during nephrectomy and poor wound healing due to suboptimal nutrition.\(^6^7,9^6\)

In patients who do not undergo nephrectomy in infancy, standard care for progressive CKD is generally adopted, including referral for dialysis or transplantation as indicated. There are, however, some unique considerations in children with ARPKD with significant dual-organ involvement. A subset of patients can require both kidney and liver transplantation, either simultaneously or sequentially. Decisions regarding timing and sequence of organ transplantation can be difficult, and Teleaga et al recently presented a clinical decision framework to help guide clinicians.

Special considerations after isolated kidney transplantation in ARPKD patients include the substantial risk of morbidity and mortality due to cholangitis/sepsis. Some authors have therefore
advocated standard use of posttransplant antibiotic prophylaxis. Other studies have suggested earlier consideration of liver transplantation (LT) in ARPKD patients with severe liver disease who are being evaluated for kidney transplantation, even if they may not otherwise meet criteria for LT-based liver disease severity alone. In patients with liver-predominant disease who first undergo LT, acceleration of kidney disease progression is also a concern. Currently, the only guidelines regarding listing for combined kidney-liver transplantation (CKLT) are in the context of end-stage liver disease due to hepatocellular dysfunction, for which listing for CKLT is recommended when estimated glomerular filtration rate is \(\leq 30\) ml/min/1.73m\(^2\). That said, the corollary of these data for patients with ARPKD who typically have biliary-related disease is unclear. Studies in patients with ARPKD who underwent CKLT have reported patient survival rates of 70% to 100%.

**SYSTEMIC MANIFESTATIONS**

**Growth Impairment**

Growth impairment has been reported in children with ARPKD; in one cohort, growth delay was observed in \(\sim 30\)% of patients. Some authors have postulated that growth retardation in ARPKD seems out of proportion to the degree of renal dysfunction, raising the question of whether there are disease-specific influences on growth. However, others have reported that growth impairment is indeed correlated with decreased renal function. Like children with other forms of CKD, children with ARPKD can successfully be treated with growth hormone.

**Neurocognitive Issues**

Behavioral and neurocognitive difficulties have been recognized as important comorbidities in children with other forms of CKD, as well as in children with hypertension, both with and without coexisting CKD. Given that children with ARPKD often have both CKD and severe hypertension during critical early years of neurodevelopment, they may be at particular risk for worse neurocognitive outcomes. A study of neurocognitive function in children with ARPKD was recently completed. This study examined results of neurocognitive testing of ARPKD patients in the Chronic Kidney Disease in Children cohort study, which includes children with mild-to-moderate CKD due to a wide range of diagnoses. Children with ARPKD were compared with a control group with renal aplasia/hypoplasia/dysplasia, matched based on kidney function, age at diagnosis, and age at study entry. In both ARPKD and control groups, scores in all domains tested were within average range, but a larger than expected proportion of children demonstrated risk for neurocognitive dysfunction (scores worse than 1 SD below the mean). Although this study did not find evidence of disease-specific neurocognitive defects in this subset of ARPKD patients with mild-to-moderate CKD, these findings may not be generalizable to children with more severe disease manifestations. Additional studies are therefore needed in ARPKD patients with a broader range of CKD and other morbidities to fully characterize their neurocognitive and behavioral functioning. However, given the presence of multiple risk factors for neurocognitive dysfunction, clinicians should maintain a high index of suspicion for neurocognitive problems and provide referrals as appropriate.

**PSYCHOSOCIAL CONSIDERATIONS**

The psychosocial impact of ARPKD on patients, families, and care providers can be far-reaching. When a diagnosis of ARPKD is suspected based on prenatal ultrasound, families face many uncertainties. Families may choose to pursue genetic testing to help guide a decision about possible pregnancy termination. Yet, as discussed previously, genetic results may not provide definitive prognostic information. Care providers must be willing to help guide families through this difficult decision-making process and to provide appropriate referrals to genetic counselors, social workers, and other sources of psychosocial support. Families may also need extra support if they are considering PGD for a future pregnancy. This can be a physically challenging procedure and can be especially emotion-laden for families who have previously faced the devastating loss of a child with severe ARPKD.

Parents may also face the decision on whether to consider testing to determine the status of asymptomatic siblings. Given that there are currently no known therapies to prevent disease progression, no consensus exists on whether testing should be offered to siblings. Providers may be called on for advice as families navigate these decisions.

Impairments in health-related quality of life have been well documented in children with CKD and ESRD. Given that children with ARPKD may also be faced with additional stressors such as liver disease, they are likely to experience similarly decreased health-related quality of life. Care from a multidisciplinary team, including child life specialists and psychologists, can be particularly helpful. Patient advocacy organizations can be extremely valuable sources of support and information for patients and families dealing with ARPKD; these include the PKD Foundation (www.pkd.org) and the ARPKD/CHF Alliance (www.aprkdcff.org).

**FUTURE DIRECTIONS AND TRANSLATIONAL CONSIDERATIONS**

To date, specific disease-targeting therapies to slow progression of ARPKD have
remained elusive. However, a number of preclinical studies have defined several potential molecular targets for therapeutic intervention (Fig 1). Studies in human ARPKD tissues have shown activation of the mammalian target of rapamycin (mTOR) pathway, suggesting a potential therapeutic role for mTOR inhibitors such as sirolimus. However, in the PCK rat model, sirolimus treatment did not slow disease progression. Studies of mTOR inhibitors in adult ADPKD patients have been disappointing despite promising results in animal studies. Thus, it seems unlikely that the current generation of mTOR inhibitors will prove effective in ARPKD.

Cyclic adenosine monophosphate (cAMP) signaling has been shown to be upregulated in ADPKD and ARPKD renal epithelia. Stimulation of the vasopressin V2 receptor (V2R) increases cAMP production, making V2R antagonists such as tolvaptan appealing as potential therapies. In the PCK rat model, V2R antagonists appear to slow renal disease progression. Additional evidence for the role of V2R signaling in ARPKD comes from experiments in which PCK rats were crossed with vasopressin knockout rats to generate double mutant progeny with varying levels of circulating vasopressin. PCK rats lacking vasopressin showed lower renal cAMP activity and almost complete inhibition of cystogenesis. Although tolvaptan has been studied in adults with ADPKD, there have been no studies in human ARPKD. Somatostatin analogs have also been studied to reduce cAMP activation in PKD. A recent study of these analogs in the PCK rat showed reduced renal and hepatic cyst formation, with pasireotide showing greater benefit than octreotide. Somatostatin analogs have been studied in adults with ADPKD, but there are no published studies in human ARPKD.

The epidermal growth factor receptor (EGFR) axis may also play a role in cyst development in ARPKD and ADPKD. Inhibition of the EGFR axis has improved biliary and renal abnormalities in various murine models of ARPKD. Therapies directed at downstream targets of both the cAMP and EGFR pathways, such as Src, may prove especially helpful; a study of Src inhibition in ARPKD mice showed improvement in both biliary and renal abnormalities.

The ultimate goal of these preclinical studies is, of course, to translate knowledge of disease mechanisms into effective therapy. However, the ability to track disease response is predicated on having defined end points, and in the case of animal studies, this has generally been serial histology. Human studies are currently hampered by the lack of defined imaging biomarkers to meaningfully track disease progression. It is therefore imperative that ongoing research efforts focus on developing reliable noninvasive biomarkers to be able to monitor the effectiveness of potential therapies.

CONCLUSIONS

ARPKD is a multifaceted genetic disorder that requires expert interdisciplinary management. Much has been learned in recent decades about the genetics and
PATHOPHYSIOLOGY OF THIS DISORDER; AND THE SURVIVAL OF PATIENTS HAS BEEN IMPROVED BY ADVANCES IN SUPPORTIVE THERAPY, DIALYSIS, AND TRANSPLANTATION. HOWEVER, MANY CHALLENGES REMAIN IN OUR UNDERSTANDING OF THE DISEASE AND IN THE CARE OF AFFECTED PATIENTS. ADVANCES IN ELUCIDATING THE FUNCTION OF THE FPC PROTEIN WILL HELP TO DEFINE ADDITIONAL THERAPEUTIC TARGETS. IMPROVEMENTS IN TECHNOLOGIES FOR NON-INVASIVE DISEASE MONITORING WILL BE INVALUABLE IN PROVIDING PREDICTIVE/PROGNOSTIC INFORMATION AND GAUGING THE EFFICACY OF ANY FUTURE POTENTIAL THERAPIES. THE ULTIMATE GOAL IS TO IDENTIFY DISEASE-SPECIFIC THERAPIES TO STOP OR EVEN REVERSE THE INEXORABLE PROGRESSION OF ARPKD-RELATED MORBIDITIES.

REFERENCES


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Erum A. Hartung and Lisa M. Guay-Woodford

Pediatrics 2014;134;e833; originally published online August 11, 2014; DOI: 10.1542/peds.2013-3646

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