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CONSENSUS EXPERT RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE: REPORT OF AN INTERNATIONAL CONFERENCE

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Abstract

Autosomal recessive polycystic kidney disease (ARPKD; MIM 263200) is a severe, typically early onset form of cystic disease that primarily involves the kidneys and biliary tract. Phenotypic expression and age at presentation can be quite variable[1]. The incidence of ARPKD is 1 in 20,000 live births[2], and its pleotropic manifestations are potentially life-threatening. Optimal care requires proper surveillance to limit morbidity and mortality, knowledgeable approaches to diagnosis and treatment, and informed strategies to optimize quality of life. Clinical management therefore is ideally directed by multidisciplinary care teams consisting of perinatologists, neonatologists, nephrologists, hepatologists, geneticists, and behavioral specialists to coordinate patient care from the perinatal period to adulthood. In May 2013, an international team of 25 multidisciplinary specialists from the US, Canada, Germany, and the United Kingdom convened in Washington, DC, to review the literature published from 1990 to 2013 and to develop recommendations for diagnosis, surveillance, and clinical management. Identification of the gene *PKHD1*, and the significant advances in perinatal care, imaging, medical management, and behavioral therapies over the past decade, provide the foundational elements to define diagnostic criteria and establish clinical management guidelines as the first steps towards standardizing the clinical care for ARPKD patients. The key issues discussed included recommendations regarding perinatal interventions, diagnostic criteria, genetic testing, management of renal and biliary-associated morbidities, and behavioral assessment. The meeting was funded by the National Institutes of Health and an educational grant from the Polycystic Kidney Disease Foundation. Here we summarize the discussions and provide an updated set of diagnostic, surveillance, and management recommendations for optimizing the pediatric care of patients with ARPKD. Specialist care of ARPKD-related complications including dialysis, transplantation, and management of severe portal hypertension will be addressed in a subsequent report. Given the paucity of information regarding targeted therapies in ARPKD, this topic was not addressed in this conference."

Keywords

ARPKD; hepatorenal fibrocystic diseases; congenital hepatic fibrosis; oligohydramnios; *PKHD1*; neurocognition

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GENETICS WORK GROUP

ARPKD Genetics

As an autosomal recessive trait, ARPKD has a recurrence risk of 25%, regardless of sex.

PKHD1* gene and fibrocystin/polyductin (FPC) protein—PKHD1* is a large gene extending over a ~500-kb genomic segment on chromosome 6p12[3]. The longest open reading frame comprises 66 exons that encode fibrocystin/polyductin complex (FPC). There is evidence for extensive alternative splicing; whether all the predicted alternative *PKHD1* transcripts are translated into proteins and what their biological functions may be it remains unknown. Overall, a critical amount of full-length protein seems to be required for sufficient biological function.

DNA-based diagnostic testing—The large size of *PKHD1* poses significant challenges to current DNA sequencing methods. Other diagnostic challenges relate to the high frequency of missense mutations and private mutations in ‘non-isolate’ populations[3]. “In cases with strong clinical and/or histopathological evidence for ARPKD, mutation detection rates of about 80–85% have been demonstrated for the patients across the entire clinical spectrum[1, 4]. Several other cilia-related disease genes may mimic ("phenocopy") ARPKD. For instance, 2% of all ADPKD patients express an early onset, severe phenotype that is clinically indistinguishable from ARPKD[5]. Finally, the phenotype of ARPKD can also be mimicked by mutations in the *HNF1B* gene, which encodes the transcription factor, hepatocyte nuclear factor-1beta (HNF1B), as well as by other gene defects that cause the hepatorenal fibrocystic diseases (HRFD; Table).

Expert opinion

- Given the high number of phenocopy disorders, 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.
- Pathogenicity predictions for missense variants represent another diagnostic challenge; caution is required when only novel or rare missense changes are detected.
- More robust next generation sequencing methods that allow simultaneous investigation of multiple cystic kidney disease genes will increasingly become available.

Prenatal genetic diagnosis

Prenatal US detection of ARPKD is often not early enough for pregnancy termination.

Expert opinion

- At present, early and reliable prenatal diagnosis is only feasible by molecular genetic analysis using single-gene testing methodologies.
- Indirect, haplotype-based linkage analysis was performed for ARPKD before complete gene sequencing was widely available. Given the possibility of misdiagnosis, linkage analysis is no longer a diagnostic method of choice.

Genotype-phenotype correlations

Genotype–phenotype correlation for *PKHD1* is hampered by a wide range of mutations, with children typically inheriting a different ARPKD mutation from each parent (compound heterozygotes)[6]. Practically all patients carrying two truncating mutations display a severe phenotype with peri- or neonatal demise, although exceptions have been reported[7]. In comparison, patients surviving the neonatal period usually bear at least one missense mutation; although the converse does not seem to apply and some missense changes can be as devastating as truncating mutations.

Expert opinion

- Caution must be exercised when predicting the clinical course from the genotype.

PERINATAL/NEONATAL WORK GROUP

Fetal Diagnostic Considerations

Expert opinion

- Standard second trimester ultrasound (US) imaging is usually sufficient to suggest the diagnosis of ARPKD, especially if findings include bilateral changes of large hyperechogenic kidneys with poor cortico-medullary differentiation.
- Macrocysts (>10 mm) in the fetal ARPKD kidney are unusual and suggest multicystic dysplasia; whereas bilateral cysts of 5–7 mm are reported in 29% of ARPKD cases[8].
- A systematic evaluation should be undertaken for extra-renal anomalies, as other fetal conditions have been associated with renal hyperechogenicity. Of particular note, mutations in *HNF1B* have been shown in some studies to be the most common cause of fetal hyperechogenic kidneys[9]. Other associations include: Turner syndrome; Trisomies 8, 13, or 18; congenital cytomegalovirus infection; acyl-CoA dehydrogenase defects (glutaric aciduria type II); and the hepatorenal fibrocystic disorders (Table).
- In the context of severe oligohydramnios, fetal magnetic resonance imaging may better delineate the renal anatomy[10].
- Amniocentesis should be considered for fetal karyotype and polymerase chain reaction for cytomegalovirus (CMV). Following transplacental passage, CMV typically infects the fetal kidney, which can result in sonographic evidence of increased renal echogenicity and oliogohydramnios in CMV-infected fetuses[11].
- A complete three-generation family pedigree should be documented, particularly adult onset renal diseases and neonatal death related to pulmonary insufficiency or renal failure.
- Ultrasonography of the parents is recommended to screen for pre-symptomatic, dominant cystic kidney diseases, such as ADPKD or *HNF1B*-related disease.

Fetal monitoring

Once a presumptive diagnosis of ARPKD is made, US should be performed every 2 – 3 weeks for serial assessment of the renal size and amniotic fluid volume. The gestational age (GA) at onset of oligohydramnios is variable in ARPKD. Onset of oligohydramnios in the second trimester may be associated with pulmonary hypoplasia and in one series, renal size >4 SD in association with oligohydramnios was associated with 100% perinatal mortality[12]. A study of 46 fetuses with severe genitourinary anomalies[13] demonstrated that after 26 weeks GA, a total lung volume value of <0.90 by magnetic resonance imaging has a sensitivity of 77.8% and specificity of 95% for predicting non-survival. A 3D US study showed that total fetal lung volume <5 %ile corrected for GA yielded a positive predictive value of 80% and a negative predictive value of 94% for lethal pulmonary hypoplasia.

Expert opinion

- Prenatal imaging does not provide precise prediction for the development of lethal neonatal pulmonary hypoplasia.

Perinatal management

After delivery, neonatal pulmonary status will usually dictate early management. When there has been a presumptive diagnosis of ARPKD, a mortality of 30–40% due to pulmonary hypoplasia has been reported[14]. Some infants with milder forms of pulmonary hypoplasia may respond well to high frequency ventilation. Persistent pulmonary hypertension (HTN) may be a prominent, but potentially reversible, component of the lung disease in the first days after birth that may respond to inhaled nitric oxide. In some cases, even extracorporeal membrane oxygenation may be appropriate if respiratory failure and/or pulmonary hypertension is not thought to be due to lethal lung hypoplasia. The potential need for dialysis in severely affected ARPKD neonates raises complex issues. Although survival of infants who initiate dialysis has improved significantly, mortality and morbidity remain concerning[15].

Expert opinion

- Patients with a presumptive diagnosis of ARPKD should be referred for delivery at a facility with a level IV NICU[16].
- Multidisciplinary prenatal consultation with input from maternal-fetal medicine, neonatology, and pediatric nephrology addressing delivery plans, neonatal respiratory illness, and short- and longer-term renal function should be arranged.
- A delivery plan should include the possibility of cesarean delivery for fetal abdominal dystocia due to renal enlargement.
- Given the lack of definitive fetal predictors of postnatal survival, decisions regarding aggressiveness of intervention both in labor and at delivery must take into account family preferences and all clinical information available at the time.
- The decision to offer (or withhold) dialysis should be made jointly by the treating physicians and the infant's parents. Peritoneal dialysis is the preferred modality[17].

RENAL WORK GROUP

General Considerations

Diagnostics—ARPKD is suggested by characteristic hepatorenal involvement and a pedigree consistent with autosomal-recessive inheritance[1].

Expert opinion

- Finding large echogenic kidneys with poor cortico-medullary differentiation bilaterally, and coexisting liver disease on standard diagnostic US imaging is usually sufficient for the diagnosis of ARPKD.

- High resolution US may improve diagnostic sensitivity, particularly in mild disease[6]. Unlike in ADPKD, kidney size/volume do not correlate with renal function in ARPKD[6].
- There may be phenotypic overlay with ADPKD and other HRFD (Table).
- In some patients, serial observation may be required to make the correct diagnosis.
- Genetic testing may facilitate the diagnosis in patients with suspected ARPKD.

Screening of siblings

Expert opinion

- ARPKD expression can be highly variable within sibships[1, 18].
- Abdominal imaging of siblings into adulthood may be appropriate[19]. Genetic testing may be helpful in defining the affectation status of even apparently asymptomatic siblings if two pathogenic *PKHD1* mutations have been identified in the index case.

Hypertension (HTN)—The prevalence of systemic HTN in children with ARPKD is 33–75%[1, 6, 18, 20]. Marked HTN is often observed in the first months of life, and neonates with systemic HTN are statistically more likely to require mechanical ventilation ($p<0.0001$)[1]. The pathogenic mechanism remains poorly understood. Limited studies in humans and animal models suggest that activation of the intra-renal renin-angiotensin-aldosterone system, without concurrent elevation in systemic angiotensin I and II levels, may play a role[21, 22]. In addition, impaired urinary dilution with associated fluid retention and dysregulation of the collecting duct epithelial sodium channel may be contributing factors to ARPKD-related systemic HTN[23, 24].

Expert opinion

- "The mainstays of current therapy are angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Combination ACEI/ARB therapy is not recommended due to increased risk of side effects, without clear added benefit. Therapy should be directed towards optimizing blood pressure control, while minimizing further reduction in GFR in the context of chronic kidney disease (CKD)[20].
- The recent multicenter ESCAPE trial in children with Chronic Kidney Disease stages 2–4 indicated that aggressive blood pressure control (target 24-hour mean arterial blood pressure below the 50th percentile for age, height and sex) may slow progression to end-stage renal disease[25]; the specific target for ARPKD has not been established.

Intracranial aneurysms—In contrast to ADPKD, intracranial aneurysms are rarely described with ARPKD[26].

Expert opinion

- There is no evidence-based association between ARPKD and intracranial aneurysms.
- Routine screening of asymptomatic patients is not warranted.

Hyponatremia—Hyponatremia is common in ARPKD, with a reported incidence of 6–26%[1, 27]. The mechanism likely involves impaired urinary dilution (rather than sodium wasting) leading to water overload, at a time when caloric and fluid intake is coupled and nutrition has a low osmotic load.

Expert opinion

- Standard treatment principles apply: in euvolemia or hypervolemia, fluid intake should be minimized without compromising nutrition, e.g. by concentrating feeds.
- Supplementation with sodium is likely to worsen HTN and should be avoided, unless there is evidence of hypovolemia.
- It is not known whether the hyponatremia is due to excessive vasopressin or tubulo-interstitial dysfunction. Thus, vasopressin receptor blockers (Vaptans) are currently not recommended.

Postnatal Management/Recommendations—Even in newborns with massively enlarged kidneys, some renal function may be preserved and may transiently improve during the first months of life[28]. Given the often difficult issues with respiratory and nutritional support, unilateral or bilateral nephrectomy has been suggested to improve respiratory status or feeding. However, the risk of accelerating renal function loss and the consequent need for renal replacement therapy early in life must be carefully weighed. Dialysis recommendations for infants are addressed above.

Expert opinion

- The rationale for unilateral nephrectomy is based on few small nutrition studies[29–31].
- There is no evidence that nephrectomy results in respiratory improvement.
- There is no evidence to support nephrectomy for severe HTN in early ARPKD.

LIVER WORK GROUP

General Considerations

Diagnostics—The primary liver disease in ARPKD is often referred to as congenital hepatic fibrosis (CHF) or ductal plate malformation and is manifest primarily by portal HTN and/or bile duct disease[32]. Portal HTN can cause splenomegaly with hypersplenism, and varices at risk for hemorrhage. Biliary disease may be very subtle, may not be appreciated by liver biochemistries or imaging studies, but can result in cholangitis. CHF is not typically associated with significant hepatobiliary inflammation or hepatic dysfunction; serum amino transferases and laboratory findings reflective of synthetic liver function (e.g. coagulation profile) are normal or near normal. Therefore, a high index of suspicion is required to recognize advancing liver disease in children with ARPKD.

Expert opinion

- In the context of known ARPKD, CHF is presumed when portal HTN is present (see below) and biochemical evidence of liver disease is minimal (i.e. serum amino transferases <2 × upper limit of normal (ULN)), liver biopsy is not indicated and extensive investigation for other causes of liver disease is not necessary. However, portal vein thrombosis should be excluded by US.
- Portal HTN is defined by splenomegaly (i.e. spleen palpable >2 cm below the left costal margin or >1 cm larger than the ULN for age[33]) and thrombocytopenia with a value <150 mm^3, or known varices, ascites, or hepatopulmonary syndrome.
- Cholangiopathy is defined by noninvasive radiologic demonstration of intra- or extra-hepatic biliary abnormalities. Of note, CHF-cholangiopathy with cholangitis may exist despite normal radiologic findings.

Anticipatory Guidance—Although uncommon, clinical manifestations of CHF (e.g. variceal hemorrhage and/or cholangitis) can be life-threatening[34], requiring a heightened awareness and anticipatory guidance for possible complications. Even though still relatively low, the risk of mortality increases if treatment is delayed. Cholangitis, in particular, may be difficult to diagnose definitively; the classical triad of fever, jaundice, and right upper quadrant pain is rarely observed in children, and other more common causes of fever in childhood are often invoked. Although there is an increased risk of hepatobiliary cancer (e.g. cholangiocarcinoma and hepatocellular carcinoma) in individuals with CHF, this dreadful complication has not been described in individuals younger than 40 years of age[34].

Expert opinion

- Hematemesis, hematochezia and/or melena require **immediate** medical attention (e.g. in an emergency facility with capacity for red blood cell transfusion).
- A high index of suspicion for cholangitis is required of those caring for ARPKD children.
- Hepatobiliary cancer is not a feature of ARPKD in childhood.

Screening—Screening for liver disease, especially complications of CHF, are warranted in children who have ARPKD. Features of portal HTN are the most frequent early manifestation of CHF and their identification permits anticipation of further complications. Liver biochemistries are not typically informative. Splenomegaly on physical examination is useful, but may be difficult to appreciate in a child with significant nephromegaly. Absence of splenomegaly does not exclude portal hypertension, however, so one should monitor for associated neutropenia or thrombocytopenia. There is no clear correlation between the severity of biliary abnormalities and the risk of cholangitis.

Expert opinion

- Care should be taken to identify splenomegaly on physical examination, with further evaluation by US (e.g. Doppler of the portal and splenic veins; measurement of maximal dimension of the spleen; and surveillance for intra- or extra-hepatic biliary dilatation).
- Annual complete blood and platelet count should be performed, with attention to the absolute counts, as well as the trends in these measurements.
- At 5 years of age, abdominal US should be performed, with attention to both intra- and extra-hepatic bile ducts and the maximal linear dimension of the spleen. If the initial studies are negative, follow up is recommended at least every 2 to 3 years.
- Suspicion for portal hypertension or biliary abnormalities should prompt a referral to a pediatric gastroenterologist/hepatologist. Once portal hypertension is verified, screening for associated complications follows standard guidelines[35].

Prophylaxis—The utility of antibiotic prophylaxis for complications of CHF is not clearly established. Ursodeoxycholic acid (UDCA), with its choleretic effect, is theoretically useful in chronic cholestasis, but this does not apply to in most cases of CHF. Furthermore, randomized, placebo-controlled studies in adults with sclerosing cholangitis have identified a previously unknown **potential** toxicity of UDCA[36]; the relevance to CHF is unknown.

Expert opinion

- Routine antibiotic prophylaxis for cholangitis is not indicated.
- Antibiotic prophylaxis for 6 to 12 weeks after a cholangitis episode, immediately following transplantation, or in the context of enhanced immunosuppression may be considered.
- Approaches to prevention and treatment of varices are similar, if not identical, to approaches used in children with portal HTN from other causes and are typically decided upon by the subspecialist.
- The use of UCDA as a choleretic cannot be recommended.

Cholangitis and Hypersplenism—Complications of biliary disease and portal hypertension in ARPKD raise important considerations for the pediatrician. A diagnosis of cholangitis often necessitates a prolonged course of intravenous antibiotics and potentially worsens the prognosis of the CHF. Recurrent cholangitis is sometimes an indication for liver transplantation. Cytopenia in the context of portal HTN may unnecessarily raise concerns, as these blood count abnormalities are not typically associated with the same morbidities as cytopenias observed with bone marrow failure or related disorders. Similarly, symptoms like abdominal pain and anorexia are sometimes attributed to pronounced splenomegaly, although a causal relationship is difficult to prove. Perhaps the most vexing issue relates to splenomegaly and concerns about splenic injury when a portion of the spleen is unprotected by the rib cage.

Expert opinion on cholangitis

- Cholangitis is a clinical diagnosis that can be difficult to definitively establish.
- Cholangitis should be considered in any ARPKD child with unexplained fever.
- An especially high index of suspicion is warranted in the first months after renal transplantation or when immunosuppression is high.
- Liver biopsy rarely yields a diagnosis of cholangitis and may represent a significant risk in the setting of biliary dilatation.

Expert opinion on cholangitis

- Hypersplenism-associated leukopenia does not typically increase infection risk.
- Splenectomy is rarely indicated as an isolated procedure.
- Limiting contact activities in individuals with a palpable spleen is highly controversial and not guided by evidence, but more by common sense.

NEUROCOGNITIVE/BEHAVIORAL WORK GROUP

In children and adolescents with ARPKD clinical features such as HTN and CKD predispose them to neurocognitive and social-behavioral challenges[37, 38]. In addition hepatic encephalopathy is well-described in individuals with renal dysfunction following portosystemic shunting (PSS) to relieve severe portal hypertension[34]; however, it is unknown whether this association occurs in patients with milder CKD. The only available pediatric study showed that children with mild to moderate ARPKD had neurocognitive functioning comparable with children with other causes of CKD across IQ, academic achievement, attention/executive functioning, and behavior[39]. To date, there is limited literature to explicitly guide clinical practice around neurodevelopmental and socialbehavioral issues in ARPKD children.

Expert opinion

- An interdisciplinary team model is suggested, that ideally would include a consulting psychologist or neuropsychologist with specialized knowledge of CKD and the associated co-morbid conditions.
- The team should engage in systematic developmental surveillance, (e.g. brief annual or biannual screenings), to track cognitive, social, and behavioral functioning over time, as well as track parent and child quality of life and adherence to medical treatment.
- Neuropsychological assessment may be indicated for those children with signs of learning/attention problems and for those who manifest behavioral/emotional difficulties.

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Table 1

ARPKD and hepatorenal fibrocystic disease phenocopies

Disease	Gene(s)	Renal disease	Hepatic disease	Systemic features	Prevalence
ARPKD	*PKHD1*	Collecting duct dilatation	CHF; Caroli disease	no	~1 in 20,000
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	yes -adults	~1 in 1,000
Nephronophthisis (NPHP)	*NPHP1-NPHP16*	Cysts at the cortico-medullary junction	CHF	+/−	~1 in 50,000
Joubert syndrome and related disorders (JBRD)	*JBTS1-JBTS20*	Cystic dysplasia; NPHP	CHF; Caroli disease	yes	~1 in 100,000
Bardet-Biedel syndrome (BBS)	*BBS1-BBS18*	Cystic dysplasia; NPHP	CHF	yes	~1 in 100,000
Meckel-Gruber syndrome (MKS)	*MKS1-MKS10*	Cystic dysplasia	CHF	yes	~1 in 140,000
Oral-facial-digital syndrome, Type I	*OFD1*	Glomerular cysts	CHF (rare)	yes	~1 in 250,000
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with *PKD1* mutations)	+/−	rare
Jeune syndrome (asphyxiating thoracic dystrophy (ATD))	*IFT80 (ATD2) DYNC2H1 (ADT3) ADT1, ADT4, ADT5*	Cystic dysplasia	CHF; Caroli disease	yes	rare
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	yes	rare
Zellweger syndrome	*PEX1-3;5–6;10–11;13;14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	yes	rare

AD – autosomal dominant; AR – autosomal recessive; CHF – congenital hepatic fibrosis