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The Spectrum of Polycystic Kidney Disease in Children

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Abstract

Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Autosomal Recessive PKD (ARPKD) are important inherited kidney diseases with distinct clinical features and genetics. While these diseases have classically been considered "adult" (ADPKD) or "infantile/pediatric" (ARPKD), it is now clear that both diseases can present in children and adults. ADPKD and ARPKD also share important pathophysiologic features, including cilia dysfunction. ADPKD is a systemic disease involving cysts in the kidneys and abdominal organs as well as abnormalities in the heart and vasculature. Although ADPKD typically presents in adults, ADPKD has been diagnosed in fetuses, infants, children and adolescents. The majority of children diagnosed with ADPKD are asymptomatic. Those with symptoms typically present with hypertension or gross hematuria. Routine screening for renal cysts in asymptomatic children who have a parent with ADPKD is generally not recommended. ARPKD is a disorder confined to the kidneys (polycystic kidneys) and liver (a developmental biliary lesion called congenital hepatic fibrosis). Although most children with ARPKD present in infancy with large, echogenic kidneys, a subset present later in childhood and even adulthood, primarily with complications related to the liver disease. As more ARPKD patients survive to adulthood, these liver complications are likely to become more prevalent.

Keywords

polycystic kidney disease; pediatric; genetic; renal cysts; congenital hepatic fibrosis

INTRODUCTION

The focus of this paper is the two forms of PKD, Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Autosomal Recessive Polycystic Kidney Disease (ARPKD). Although they share important pathophysiologic features, the two diseases have distinct clinical and genetic features (Table 1).

ADPKD is a systemic disease that includes not only polycystic kidneys but also abnormalities in other abdominal organs (liver, pancreas and intestinal tract) as well as in the heart and vasculature.[1] ADPKD has previously been termed "adult" polycystic disease. This

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term, however, is a misnomer. While the majority of ADPKD patients are diagnosed in adulthood, it is now well-recognized that ADPKD can present in children of all ages from fetuses to adolescents.[2, 3]

ARPKD is a disorder that primarily affects only two organs, kidney (polycystic kidneys) and liver (congenital hepatic fibrosis).[4] Additional abnormalities, such as pulmonary hypoplasia, generally occur as the result of the oligohydramnios (Potter's) sequence. ARPKD has historically been referred to as "infantile" polycystic kidney disease. This nomenclature, however, does not reflect current knowledge about the genetic basis of the disease (autosomal recessive inheritance) or the fact that a subset of ARPKD patients may present in adolescence and even adulthood.[5] Thus, ARPKD is now the preferred term to describe this distinct inherited disorder.

Both ADPKD and ARPKD kidney disease are characterized by cystic dilatations of the renal tubules. In ADPKD, cysts can show massive expansion over time, eventually pinching off and becoming discontinuous with the urinary stream. It is estimated that only 1% of nephrons become cystic. In addition, cysts can occur anywhere along the nephron, although recent studies suggest that the majority of cysts are collecting tubule in origins. In contrast, ARPKD cysts are exclusively collecting tubule in origin and are generally much smaller (typically "microcysts", not visible on gross examination). In ARPKD, all of the collecting tubules are involved and are manifest as fusiform dilatation radiating from cortex to medulla.

There are a number of other cystic kidney disorders that may present with clinical features similar to ADPKD or ARPKD (Table 2). Many of these inherited disorders (such as nephronophthisis and Biedl-Bardet syndrome) as well as ARPKD and ADPKD are now termed "ciliopathies." This term has arisen from the recognition that these clinically diverse diseases share many important pathogenetic features related to the primary cilia (see discussion below). Over 25 ciliopathy genes associated with renal diseases have been identified. Several recent reviews provide detailed information about the genetic basis for these related disorders. [6–8]

EPIDEMIOLOGY, GENETICS AND PATHOGENESIS OF ADPKD AND ARPKD

ADPKD

ADPKD is the most common inherited kidney disease, occurring at an incidence of approximately 1:1000. As its name implies, it is inherited as an autosomal dominant trait. However, there is considerable phenotypic variability, even within the same family. Males and females are affected equally and ADPKD is present in all races and ethnicities. While it is a very rare case of end-stage renal disease (ESRD) in children, it accounts for approximately 5% of ESRD in adults.

ADPKD is caused by mutations in one of two genes, *PKD1* and *PKD2. PKD1* mutations account for approximately 85% of ADPKD.[9] It is a very large, complex gene (46 exons) located on chromosome 16p13. This complex structure has made it challenging to identify mutations or to determine which variants actually are pathogenic. *PKD1* encodes the protein, polycystin 1 (PC1), is a large membrane bound protein with receptor-like properties that interacts with polycystin 2 (PC2), the protein product of *PKD2*. PC1 is expressed throughout the body, including abdominal organs (kidney liver, pancreas), heart and vasculature. Its widespread expression helps explain the multi-organ system phenotype. *PKD2* is a smaller gene (15 exons) located on chromosome 4q21-q23. *PKD2* mutations account for only 15% of ADPKD. Its product, PC2, is a cation channel that modulates the concentration of intracellular calcium, an important determinant of several downstream

signaling processes. Approximately 10% of ADPKD patients will not have a positive family history of ADPKD and are presumed to have a new genetic mutation.

ADPKD can also be a component of the inherited disease, tuberous sclerosis (TS). One of the causative genes, *TSC2*, lies adjacent to the PKD1 gene on chromosome 16. In some TSC2 patients, the mutation is large enough to encompass both genes, resulting in a "contiguous gene syndrome" Affected patients have features of both ADPKD and TS.[10]

ARPKD

In contrast to the relatively frequent occurrence of ADPKD, ARPKD is much rarer. It is estimated to occur in 1:10,000–1:40,000 live births. However, these numbers may underestimate the true incidence since the most severely affected infants may not survive beyond the first few days of life (primarily due to respiratory causes) and may not receive a definitive diagnosis. ARPKD is inherited as an autosomal recessive trait, occurs in all ethnicities and affects males and females equally. Unlike ADPKD, there is far less phenotypic variability within families.

ARPKD is caused by mutations in the *polycystic kidney and hepatic disease 1* gene (*PKHD1*), located on chromosome 6p21.[11, 12] *PKHD1* is a very large gene (12 kb of mRNA spanning at least 66 exons), that can form multiple alternative mRNA transcripts. The gene encodes the protein, fibrocystin/polyductin (FPC). Like PC1, FPC is a membrane-bound protein whose function is poorly understood but may also function as a receptor. Mutations have been reported throughout *PKDH1*, with no predominant mutation identified. Most families, in fact have a unique, "private" mutation.[13]

Pathophysiology of ADPKD and ARPKD

An important key to our understanding of the common pathophysiology of PKD has been emerging recognition of the central role of abnormal cilia structure and/or function.[14, 15] The primary cilium is an organelle, once thought to be vestigial in nature, that is present on the apical (non-blood) side of almost epithelial cells as well as many endothelial cells throughout the body. The central role of cilia dysfunction has led to this group of disorders being designated the "ciliopathies."[8] Numerous studies in both animals models and human patients with ARPKD and ADPKD have demonstrated that the majority of the PKD related proteins are located on or in close proximity to the cilium and its associated centrosome.[16]. The primary cilia are thought to function as mechanosensors that translate mechanical signals (e.g. fluid flow) into chemical signals within epithelial and endothelial cells. [17–19] Cilia dysfunction has been implicated in a number of processes that can impact cyst development and expansion, including intracellular calcium regulation and sodium transport. [20, 21] Cilia dysfunction has also been implicated in kidney morphogenesis as well as maintenance of a healthy epithelial and endothelial layer. Specifically, the importance of the cilia in maintaining planar cell polarity (PCP) has been highlighted by a number of recent studies.[15] PCP is a key process by which cells are able to form monolayers, migrate and orient themselves during cell division and proliferation.

A growing body of literature has provided support for a central role of cyclic adenosine monophosphate (cAMP) in the pathogenesis of diverse forms of PKD. cAMP is a second messenger for multiple signaling pathways [22] and promotes both fluid secretion and cell proliferation. Increased cAMP is a feature of human ADPKD kidneys and several PKD animal models. cAMP can be activated by a number of receptor/ligand complexes. In the collecting tubule, the vasopressin V2 receptor (V2R), which mediates vasopressin responsiveness, is a major activator of cAMP. Binding of V2R by vasopressin causes increased levels of intracellular cAMP to promote insertion of aquaporins (water channels)

in the apical membrane of the cell. Multiple other downstream cAMP-dependent pathways can also be activated. Cystic kidneys from several model show increased V2R activity (evident by increased AQP2 and cAMP activity), and treatment with specific inhibitor of V2R (tolvaptan, see below), ameliorated and even reversed cystic kidney disease progression in several cystic kidney disease animal models.[23]

Other factors that have been implicated in cyst pathogenesis include members of the epidermal growth factor (EGF) family and its related receptors, ErbB1 (EGFR), ErbB2 and ErbB4.[24] Growth factor/receptor expression is increased in cystic kidneys compared to age-matched kidneys, prompting some to speculate that it reflects a reversion to a more immature cellular phenotype. Genetic or pharmacologic intervention of the EGF ligand/EGFR axis has been shown to improve cystic kidney disease in ARPKD and ADPKD animal models. Unfortunately, the potential toxicities of these compounds may limit their applicability to human studies. Another potential mediator of cell proliferation is the mammalian target of rapamycin (mTOR) pathway. mTOR is a cytoplasmic protein that promotes cell growth, proliferation and de-differentiation. It forms a complex with tuberin, the protein product of TS2 and PC1.[25] mTOR activity is increased in human and animal models of PKD and treatment of two animal models of PKD with rapamycin (an mTOR inhibitor) decreased cyst formation.

CLINICAL FEATURES AND MANAGEMENT OF ADPKD

Clinical Presentation

Although patients with ADPKD often do not develop symptoms until adulthood [26], it is important to emphasize that ADPKD can present at any age. [3, 27, 28] In the fetus or neonate, ADPKD may mimic ARPKD (large echogenic kidneys without discrete cysts) or can present with the typical appearance of macroscopic cysts.[5] Patients diagnosed during this period are not necessarily symptomatic and may be diagnosed by prenatal screening ultrasound. Those diagnosed later in childhood are often discovered to have renal cysts incidentally while undergoing an imaging study for other indication (such as a CT scan to evaluate for possible appendicitis). Alternatively, they may be diagnosed as part of an evaluation for gross hematuria or hypertension. The latter is the most common and, typically the earliest, presenting sign of ADPKD. Additional signs and symptoms prompting evaluation and diagnosis can include urinary tract infection or urolithiasis. Flank pain from enlarging kidneys or cyst hemorrhage is typically not a presenting symptom in children. Despite the fact that ADPKD is a systemic disease involving multiple organs, pediatric patients often do not exhibit extra-renal signs or symptoms, although these have been reported in children even at a very young age.[29, 30]

Diagnosis

Ultrasonography is the most common imaging modality used to diagnose ADPKD. As with affected adults, the typical ultrasonographic appearance of ADPKD in children is the presence of renal cysts. It is not uncommon for children to show asymmetric involvement or even isolated unilateral cysts.[31] In adults at 50% risk for ADPKD (i.e. those with an affected parent), specific diagnostic ultrasonography criteria have been established.[32] The “Ravine criteria,” which were recently updated, are used to diagnosis ADPKD based on the number of cysts in each kidney at certain ages.[33] However, no such criteria have been developed for at-risk children. Because simple cysts are rare in children, the finding of even one cyst in a patient at-risk for ADPKD is considered diagnostic by some.

In the instance where there is no family history of ADPKD, the diagnosis may be more challenging, although it is strongly suggested by the presence of multiple cysts on both kidneys. In order to facilitate definitive diagnosis and assess potential risk for siblings,

screening ultrasonography of both parents is recommended. Parents may be asymptomatic or may carry the diagnosis of primary (essential) hypertension. It is important to note that the finding of a normal ultrasound in a parent less than 30 years of age may not preclude the diagnosis and ultrasonography of the grandparent may be indicated. In fact, a small set of adults with ADPKD were diagnosed with the disease after cystic kidneys were identified in their child (or grandchild).

Genetic testing, primarily in the form of gene sequencing for identification of mutations, is available. However, it is not necessary in patients who have a positive family history of ADPKD and typical radiographic appearance of bilateral renal cysts. Mutation analysis, even in those families known to have ADPKD may only detect 85% of mutations and will not change clinical management. The one instance when it can be helpful is in excluding (or including) family members as potential kidney donors when considering living donor candidates for an ADPKD transplant recipient.

The issue of performing screening ultrasonography on asymptomatic children who have a parent with ADPKD remains controversial. Because there are currently no disease specific therapies, it is generally recommended that asymptomatic children not undergo screening. Both financial and psychosocial considerations need to be taken into account if a positive result is found. In addition, there is the potential that a negative ultrasound could be falsely reassuring. For these reasons, if a parent with ADPKD requests screening of their at-risk child because they “need to know,” it is strongly advised that they receive genetic counseling before any screening is performed. At risk children should have yearly monitoring for hypertension or urinary abnormalities (such as hematuria or proteinuria), and additional evaluation considered if those develop.

Complications and Treatment

As noted above, there are currently no disease-specific therapies available for ADPKD, although several novel therapies are in clinical trials as discussed below. Currently, treatment is directed at managing or preventing complications of the disease. Hypertension is a common and early presenting feature of the disease and eventually develops in the vast majority of patients. Left ventricular hypertrophy may be evident in adolescents/young adults even before overt hypertension is present, likely reflecting the underlying vascular abnormalities that are a primary feature of the disease. [34] Mitral valve prolapse (MVP) also occurs in up to 15% of children and adults with ADPKD [35, 36]. Dysregulation of the renin-angiotensin system (RAS) is thought to be a major mediator of hypertension in ADPKD, possibly through cyst compression causing local ischemia and RAS activation. [37, 38] Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are considered the treatments of choice for hypertension in ADPKD patients. Whether these agents together provide any additive benefit is currently being studied in the large, multicenter, HALT-PKD trial.[39]

Hematuria is a common complication of ADPKD and may affect up to 40% of patients. Gross hematuria (either painful or painless) can occur after seemingly minor trauma and may be the presenting symptom that prompts radiographic evaluation. Hematuria may be the result of cyst hemorrhage, urinary tract infection, urolithiasis and, less commonly, malignancy.

Urinary tract infection is common in ADPKD and typically present with fever and flank pain. However, because the cysts can become disconnected from the urinary stream and can function as an abscess. Persistent fever and flank pain should raise the question of an infected cyst, as the urine culture in these instances may not be positive. Positron emission tomography (PET) scan has been reported to be superior to other imaging modalities (e.g.

ultrasound and CT scan) in diagnosing infected cysts.[40] It is important to note that certain antibiotics commonly used to treat UTIs (specifically beta-lactam penicillins and aminoglycosides) show poor cyst penetration and should not be used for coverage of suspected UTI/cyst infection. Fluoroquinolones, on the other hand, show good cyst penetration and should be considered as first line therapy. In some instances, persistently infected cysts require laparoscopic drainage.

Flank pain is a potentially debilitating complication of ADPKD, but is less common in children than adults.[41] Causes of flank pain are similar to those outlined for hematuria. Management includes identifying potential treatable causes (e.g. infection, urolithiasis). Medical therapies include non-steroidal anti-inflammatory agents and short term narcotic treatment. Long term narcotic use is generally not recommended and referral to a pain specialist may be indicated. Surgical options include laparoscopic cyst drainage, sclerotherapy, decortication (unroofing of the cyst) or denervation. Nephrectomy should be considered only as a last resort in these instances.

Hepatic cysts/polycystic liver disease (PLD) are relatively common in adults but, even when present in children, typically do not cause symptoms. Severe forms of PLD are rare and occur almost exclusively in adult women. Patients with PLD typically retain normal hepatic function and only rarely require liver transplantation. Congenital hepatic fibrosis is a rare occurrence in ADPKD.[42]

Cerebral aneurysms are a dreaded complication of ADPKD. It is estimated that the overall incidence (as detected by magnetic resonance angiography, MRA) is about 10% in asymptomatic adult ADPKD patients. Though rare, clinically significant cerebral aneurysms have been reported in ADPKD children.[43] Patients with a family history of aneurysms have a five-fold increased risk of developing them than those without a family history (25% versus 5%). In the general ADPKD population (those without a family history), routine MRA screening is usually not recommended in asymptomatic patients. However, it is recommended in those with symptoms or in high risk occupations (e.g. airplane pilots).

A number of therapies have been studied in animal models in an effort to identify treatments that can slow progression of the kidney and/or liver disease in ADPKD. Specific nutritional interventions shown to be beneficial in animals have included avoidance of caffeine (which can stimulate cAMP activity) and consumption of soy based protein or flaxseed. Increased water consumption, which suppresses V2R activity, has also been found to be beneficial in an animal PKD model. None of these interventions, however, have been well studied, or proven to be effective in human ADPKD patients.

Several novel pharmacologic therapies, targeted at specific pathogenic processes that promote cystic kidney or liver disease progression, have shown promise and animal models of PKD.[44] Three of these have been studied or are currently being studied in Phase III trials in adult ADPKD patients. Tolvaptan is a novel V2R inhibitor that was recently FDA-approved for treatment of refractory hyponatremia. Phase II studies suggested that it was well tolerated and it is now being studied in an ongoing industry-sponsored Phase III trial in the US, Europe and Asia. Octreotide is a somatostatin agonist that inhibits cAMP signaling in both the liver and the kidney. It is FDA-approved for treatment of several gastrointestinal disorders. It is currently being studied in ADPKD patients in a Phase III trial. Sirolimus and everolimus are mTOR inhibitors that have been in use for several years as immunosuppressants for solid organ transplants. The results of two large scale clinical trials involving these agents in the treatment of ADPKD patients were recently reported.[45, 46] Unfortunately, the findings were not encouraging. Sirolimus failed to impact kidney growth; and, although everolimus slowed kidney growth, it did not slow decline in renal function.

Prognosis

Approximately 50% of patients with ADPKD will progress to end-stage renal disease (ESRD), although the age at which this occurs varies. Patients with PKD1 mutations generally reach ESRD at an earlier age than those with PKD2 mutations (53 years versus 69 years). However, because of significant variability in the severity and clinical course of the disease, identifying whether a patient has a *PKD1* or *PKD2* mutation is generally not helpful in predicting the clinical course of an individual patient. Although data about children with very early onset ADPKD are limited, recent studies suggest that the prognosis may be more favorable than expected, with renal function preserved through most of childhood.[47] It has been reported that children and adolescents with certain clinical findings, such as hypertension, hematuria, heavy proteinuria or enlarged kidneys may be at increased risk for more rapid disease progression.[47] Despite the high likelihood of progression to ESRD as adults, the vast majority of pediatric patients with ADPKD will have normal renal function throughout childhood.

CLINICAL PRESENTATION, DIAGNOSIS, COMPLICATIONS AND TREATMENT OF ARPKD

ARPKD patients typically present as neonates (or prenatally) with evidence of kidney disease and/or its sequelae (notably oligohydramnios and resulting pulmonary hypoplasia). As many as one half are now diagnosed prenatally.[48] Presenting features in neonates and infants include large palpable flank masses and variable degrees of respiratory distress (related to the pulmonary hypoplasia). [4] Hypertension can be severe and occurs early. Clinical evidence of hepatic disease (e.g. hepatomegaly) may be absent in over 50% of newborns with ARPKD, despite the fact that the liver lesion is always present on microscopic examination.

In contrast to the neonatal/infant presentation, a small but important subset of ARPKD patients may present later in childhood, or even in adulthood.[48] This latter group typically presents with symptoms related to the hepatic disease (congenital hepatic fibrosis, CHF), rather than the renal disease. CHF (alternatively called Caroli's disease) is biliary ductal plate malformation characterized by periportal fibrosis and bile duct proliferation with normal hepatocyte structure and function. Clinical presenting signs and symptoms in this older cohort include hepatomegaly, and evidence of portal hypertension (e.g. splenomegaly, variceal bleeding). [49, 50] A recent series showed that almost one-third of individuals with mutations in *PKHD1* and hepatic involvement were 20 years or older at the time of initial presentation, suggesting that the clinical spectrum of the disease is broader than previously appreciated. [51]

Diagnosis

The diagnosis of ARPKD is generally made on the basis of clinical criteria, which include the presence of enlarged, echogenic kidneys typical of ARPKD, as well as one or more additional findings (the absence of renal cysts in both parents, history of a previously affected sibling, parental consanguinity or clinical, laboratory or pathologic features of hepatic fibrosis).[4] It is important to confirm that the parents (or grandparents, if the parents are under 30 years of age) do not have renal cysts, because the presentation of ADPKD in the neonatal period may be indistinguishable from that of ARPKD.[5]

In the neonatal period, renal ultrasonography demonstrates markedly enlarged echogenic kidneys, reflecting the presence of numerous microscopic cysts not discernible by ultrasound. "Macroscopic cysts," more typical of ADPKD, are usually absent in the neonatal period. Over time, ARPKD kidneys may take on an appearance more typical of ADPKD,

with macroscopic cysts evident. The hepatic ultrasound may be normal in the newborn and young child. Abnormalities, when present, include hepatomegaly, varying degrees of splenomegaly, increased liver echogenicity and poor visualization of peripheral portal veins. Macroscopic liver cysts, a more common finding in ADPKD, occur only rarely in ARPKD, although choledochal cysts have been reported.

Genetic diagnosis is possible either through linkage analysis (in families who have already had an affected child) or through direct mutation. Because of the genetic complexity of *PKHD1*, mutation analysis via gene sequencing only detects mutations in 60–75% of patients with known ARPKD. Liver and/or kidney biopsies are rarely done for diagnostic purposes but may be indicated in patients for whom the diagnosis is not clear.

Complications and Treatment

Short term complications of ARPKD in the neonatal period include respiratory distress, fluid and electrolyte imbalance, oliguria, acute kidney injury and hypertension.[4] As with ADPKD, there are no disease-specific treatments for ARPKD and treatment is focused on minimizing and treating the long-term complications of the kidney and liver disease. These include hypertension, chronic kidney disease (and its associated complications), and portal hypertension, varices, ascending cholangitis and liver failure requiring transplantation.[48] Chronic lung disease and growth retardation are also complications, although these may become clinically less significant in adolescence and adulthood.

Hypertension may be severe and occurs early in the course of disease. ACE inhibitors are considered the treatment of choice in ARPKD patient, although they have never been formally studied. Studies in an ARPKD animal model, however, suggest that increased RAS activation is a feature of cystic kidney disease.[52] Many ARPKD patients require several medications to control blood pressure.

Management of chronic kidney disease in children includes monitoring and treatment of metabolic derangements (hyperkalemia, metabolic acidosis, anemia, metabolic bone disease), as well as close attention and optimization of nutrition and growth. Feeding difficulties are common in pediatric patients with CKD in general and in ARPKD patient, in particular. In young children, feeding may be hampered by massively enlarged kidneys causing impingement on the stomach and resulting in early satiety and the development of gastroesophageal reflux. Enteral feedings via nasogastric or gastrostomy tubes are often needed to ensure delivery of sufficient calories. In some instances, unilateral or bilateral nephrectomies have been performed because of severe feeding intolerance and/or respiratory distress associated with massive kidney enlargement. [53, 54]

Patients with ARPKD may have evidence of hematuria, but gross hematuria and cyst bleeding do not occur as they do in ADPKD patients. Similarly, because the kidneys do not show progressive, massive enlargement over time, flank pain related to cyst growth is also not seen. ARPKD patients can develop urinary tract infections. However, unlike ADPKD in which cysts become disconnected from the urinary stream and cyst infection can be a major concern, in ARPKD patients, UTIs can generally be treated with standard medications (based on the culture result) without concern for cyst wall penetration.

With the advances in renal replacement therapy and improved patient survival, complications of the congenital hepatic fibrosis (CHF, also called Caroli's disease) are becoming more prominent and may dominate the clinical picture in adolescents and adults. [48, 55] Almost half of the neonatal survivors will develop evidence of portal hypertension over time.[56] However, synthetic function and transaminases often remain normal until disease is very advanced. Early referral to a hepatologist is warranted in any

patient with clinical evidence of liver disease (e.g. hepatomegaly). Patients require yearly monitoring by their hepatologist for any complications associated with portal hypertension, even if they remain asymptomatic. [57, 58] Patients with CHF are at risk for life-threatening ascending cholangitis, which may occur at any time, even as early as a few weeks of age.[59] Fever with upper quadrant pain and/or elevation of transaminases or biliary markers (e.g. GGT), should lead to prompt evaluation and initiation of antimicrobial therapy. Not all CHF patients present with classic findings of cholangitis; a small subset may manifest the disease as unexplained recurrent sepsis with gram negative organisms.[60]. In patients who have a history of ascending cholangitis, chronic prophylaxis with trimethoprim/sulfamaxazole is often recommended.

Periodic endoscopy is recommended to identify and monitor the severity of esophageal varices. Esophageal banding of large varices may be performed. In the past, the more severe cases of portal hypertension have been treated with porto-systemic shunts. However, several case studies have reported the occurrence of hepatic encephalopathy in patients with shunts who subsequently progressed to end-stage renal disease.[58] The precise mechanism for the encephalopathy is not known. The spectrum of complications has prompted many centers to proceed directly to liver transplantation in patients with recurrent cholangitis or those being considered for porto-systemic shunts.[61, 62] Combined liver-kidney transplantation has also been recommended for those with CKD and significant liver involvement.

An additional complication of CHF is splenomegaly, causing anemia, thrombocytopenia and leukopenia. While these findings by themselves may not be clinically significant, they can impact tolerance of immunosuppressive therapy and/or anti-viral therapy post-kidney transplantation. Patients with CHF are also at increased risk of cholangiocarcinoma.[8].

Prognosis

Although ARPKD was once thought to be uniformly fatal at birth, mortality in the neonatal period is estimated to be 30%, primarily related to severe pulmonary hypoplasia. Ten-year patient survival of those who survive the neonatal period is estimated to be about 80%.[49] Patients who survive the neonatal period typically develop progressive renal dysfunction and a significant proportion (>30%) will progress to ESRD in the first decade of life. An additional 20–30% will progress during adolescence. Overall renal survival rate is only 42% by adulthood [56].

The long term liver prognosis in ARPKD patients is more difficult to predict, since studies are limited and many of the neonatal survivors have not yet reached adulthood. What is clear is that with the success of renal transplantation and improved survival of these infants into adulthood, complications related to CHF as discussed above are likely to become an increasingly common cause of morbidity and mortality with age. It is concerning that in a small series of ARPKD patients who had undergone a kidney transplant, 80% developed clinically significant hepatic complications, some of which were direct contributors to an increased risk of mortality.[63] Thus, early identification and referral for treatment of the hepatic complications is imperative.

SUMMARY/CONCLUSIONS

ADPKD and ARPKD are both inherited renal diseases that have distinctive patterns of inheritance, gene defects, clinical features and complications. Studies in animal models have also highlighted a shared pathophysiology between these distinct clinical disorders as well as other forms of PKD. These shared features suggest that treatments that are potentially efficacious in one disease may also be useful in the treatment of the other. Unfortunately, disease specific treatments are not yet available and treatment for both ADPKD and ARPKD

in adults and children is focused on identifying and minimizing the renal and extrarenal complications. Thus, it is important for practicing adult and pediatric nephrologists to have a clear understanding of the disease specific complications of ADPKD and ARPKD so that appropriate care can be given to affected adults and children.

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Key points

- ADPKD and ARPKD can present at any age from infancy to adulthood;
- ADPKD, ARPKD and other “ciliopathies” share common pathophysiologic features, including abnormal cilia structure and/or function and increased cAMP signaling, which contribute to cystic cell proliferation, fluid secretion and changes in the extracellular matrix;
- Survival of pediatric ARPKD and ADPKD patients into adulthood is now the norm; thus, both adult and pediatric nephrologists should become familiar with the distinct renal and extrarenal complications of these two diseases.

Table 1

Genetic and (Typical) Clinical Features of ARPKD and ADPKD

Disease Feature	ARPKD	ADPKD
Disease causing gene/Protein	PKHD1/fibrocystin	PKD 1/polycystin 1 PKD2/polycystin 2
Pattern of Inheritance	Autosomal recessive	Autosomal dominant
Family History of PKD	Absent (unless prior affected sibling)	Usually present (but absent in 10% of patients, who have new mutations)
Age of presentation	Neonate/infant	Adolescent/adult
Asymptomatic presentation	Rare	Common (especially in childhood)
Enlarged kidneys	Present	Common (in adulthood), variable in childhood
Macroscopic cysts on ultrasonography	Absent or few (may develop later in childhood)	Present
Hypertension	Present	Common
Urinary concentrating defect	Present	Present
Hematuria	Typically absent	Common (microscopic or macroscopic)
Flank Pain	Rare	May be present
Urolithiasis	Rare	May be present
Hepatosplenomegaly/Portal hypertension	May be present	Very rare
Extra-renal cysts	Absent	Common(in adulthood)
Vascular abnormalities (Cerebral or aortic aneurysms, mitral valve prolapse)	Absent	May be present
Progression to ESRD	Over 60% by adulthood	50% lifetime risk, usually in the 5^{th}–7^{th} decades of life

Table 2

Causes of Renal Cysts in Children

Polycystic Kidney Disease (PKD)
Autosomal recessive polycystic kidney disease (ARPKD)
Autosomal dominant polycystic kidney disease (ADPKD)
Glomerulocystic kidney disease (GCKD)
Other Inherited or Syndromic Diseases Associated with Polycystic Kidneys
Tuberous sclerosis complex (contiguous gene syndrome)
Bardet-Biedl syndrome
Juvenile Nephronophthisis
Meckel-Gruber syndrome
Oro-facio-digital syndrome, Type I
Von-Hippel Lindau syndrome
Jeune syndrome
Beckwith-Wiedemann syndrome
Short-rib polydactyly syndrome
Sporadic Disorders
Multicystic dysplastic kidney
Isolated diffuse cystic dysplasia
Caliceal diverticuli
Unilateral cystic kidney disease
Simple renal cyst*
Acquired cystic kidney disease*

*Rare in children