Cystic Kidney Disease: A Primer

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Renal cystic diseases encompass a broad group of disorders with variable phenotypic expression. Cystic disorders can present during infancy, childhood, or adulthood. Often, but not always, they can be distinguished by the clinical features including age at presentation, renal imaging characteristics, including cyst distribution, and the presence/distribution of extrarenal manifestations. It is important to take the clinical context into consideration when assessing renal cystic disease in children and adults. For example, solitary kidney cysts may be completely benign when they develop during adulthood but may represent early polycystic kidney disease when observed during childhood. In this review, we have categorized renal cystic disease according to inherited single-gene disorders, for example, autosomal recessive polycystic kidney disease; syndromic disorders associated with kidney cysts, for example, tuberous sclerosis complex; and nongenetic forms of renal cystic disease, for example, simple kidney cysts. We present an overview of the clinical characteristics, genetics (when appropriate), and molecular pathogenesis and the diagnostic evaluation and management of each renal cystic disease. We also provide an algorithm that distinguishes kidney cysts based on their clinical features and may serve as a helpful diagnostic tool for practitioners. A review of Autosomal Dominant Polycystic Disease was excluded as this disorder was reviewed in this journal in March 2010, volume 17, issue 2.

Key Words: Polycystic kidney, Nephronophthisis, Glomerulocystic, Tuberous sclerosis, Bardet-Biedl

RENAL CYSTIC DISEASES ASSOCIATED WITH SINGLE-GENE DEFECTS

Autosomal Recessive Polycystic Kidney Disease

Disease Characteristics. Autosomal recessive polycystic kidney disease (ARPKD, MIM 173900) is a severe hepatorenal fibrocystic disorder characterized by nonobstructive dilatation of the kidney collecting ducts and malformation of the portobiliary system. It occurs with an estimated frequency of 1 in 20,000 live births.[1] ARPKD is typically diagnosed in utero or at birth and manifests as progressive renal insufficiency and portal hypertension. The typical kidney phenotype consists of enlarged echogenic kidneys with loss of corticomedullary differentiation because of fusiform dilatation of the collecting ducts. Affected fetuses often have oligohydramnios leading to fetal constraint and the "Potter sequence" that consists of characteristic dysmorphic facies, pulmonary hypoplasia, and limb defects. The estimated perinatal mortality rate is 30% because of respiratory insufficiency.[2,3] In patients who survive the first month of life, 1-year survival rates of 92% to 95% have been reported.[1]

The clinical course of infants who survive the neonatal period is characterized by severe systemic hypertension, progressive renal insufficiency, and portal hypertension. Although the pathophysiology of underlying hypertension is unclear, at least 1 study demonstrates intrarenal Renin-angiotensin-aldosterone system activation.[4] Infants often have hyponatremia, presumably because of defects in free water excretion.[4] Most ARPKD patients progress to ESRD, although the age of onset is variable. The kidney survival rate of 1 large cohort of neonatal survivors was 86% at 5 years and decreased to 42% at 20 years.[2] Age of ESRD onset is somewhat correlated with age at ARPKD diagnosis.[5]

Histologic liver involvement is invariably present in all ARPKD patients and is characterized by defective remodeling of the ductal plate with intrahepatic duct dilatation and progressive portal tract fibrosis.[1] Portal hypertension is the predominant clinical manifestation and may cause gastroesophageal varices and hypersplenism.[1] Splenomegaly may further result in thrombocytopenia, leukopenia, and anemia with the potential for splenic dysfunction and predisposition to bacterial infections. ARPKD patients with extensive dilatations of intrahepatic and extrahepatic bile ducts are at increased risk of ascending bacterial cholangitis.[1] Because hepatocytes are not involved, hepatocellular dysfunction is rare and liver enzymes are characteristically not increased.

Genetics and Molecular Pathogenesis. ARPKD is caused by mutations in the polycystic and hepatic disease gene 1 (*PKHD1*) that encodes fibrocystin-polyductin complex (FPC), a protein expressed in primary cilia of kidney and bile duct epithelial cells.[3,6,7] *PKHD1* is an exceptionally large gene that spans approximately 470 kb of genomic DNA and consists of 86 exons, with 67 exons included in the longest open-reading frame transcript.[7] A number of alternatively spliced transcripts have been identified; however, the exact function and clinical significance of these isoforms have not been elucidated.[8] Almost 750 pathogenic *PKHD1* mutations have been identified to date (http://www.humgen.rwth-aachen.de/), with approximately 44% classified as missense mutations.[9,10] A small number of relatively common mutations (eg, p.T36 M) account for ~10% of all *PKHD1* pathogenic variants.[11] Most affected patients are compound heterozygotes, carrying 2 different mutant alleles.[12]

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Phenotype-genotype studies suggest that patients carrying a truncating mutation on both parental alleles have a more severe phenotype leading to perinatal demise.[10,13,14]

However, there are notable exceptions, for example, a child homozygous for a large *PKHD1* deletion who survived well past the neonatal period.[15] Although most missense mutations are associated with milder disease, a number of missense mutations result in severe phenotypes when present with a truncating mutation or in the homozygous form.

FPC is a 4074-amino acid transmembrane protein predominantly expressed in kidney cortical and medullary collecting ducts and thick ascending loops of Henle and ductal structures in the liver and pancreas.[16] FPC has been identified as a structural component of primary cilia in kidney tubular epithelial cells and cholangiocytes of bile ducts.[7,17-19] The specific functions of FPC remain to be fully characterized. However, numerous other proteins associated with other hepatorenal fibrocystic diseases (eg, autosomal dominant polycystic kidney disease [ADPKD], nephronophthisis [NPHP], Meckel-Gruber, Joubert, Bardet-Biedl, and other ciliary chondrodysplasias syndromes) also localize to the primary cilia/basal body (Fig 1), suggesting a role for primary cilium in the development and maintenance of kidney tubular architecture.[1]

Diagnosis and Management. Sonographic features of ARPKD include enlarged, echogenic kidneys with poor corticomedullary differentiation. Dilated cortical collecting ducts just under the kidney capsule may be visible with high-resolution ultrasound (US). The cortex is often compressed to the periphery by the dilated medullary collecting ducts, forming a hypoechoic halo.[20]

Macrocysts are not routinely present at birth. Furthermore, kidney size in ARPKD stabilizes or may decrease over time and does not show progressive macrocystic enlargement as in ADPKD.[1]

It can be difficult to differentiate ARPKD from ADPKD, in that a subset of ADPKD patients may present in infancy or early childhood with enlarged echogenic kidneys. Likewise, ARPKD can present in older children, who may demonstrate kidney macrocysts that can mimic the kidney cysts of ADPKD.

ARPKD kidneys in utero are hyperechoic and display "decreased" corticomedullary differentiation because of the hyperechoic medulla. In comparison, ADPKD kidneys in utero tend to be moderately enlarged with a hyperechoic cortex and relatively hypoechoic medulla causing "increased" corticomedullary differentiation.[20] In addition, high-resolution US can detect the dilatations of branching collecting ducts that are readily distinguished from the round cysts of ADPKD.[20] Renal US evaluation of the parents may be useful. Absence of cysts in the parents (particularly if they are >30 years) suggests ARPKD rather than ADPKD.[20,21] However, it is important to note that in 5% to 10% of patients, ADPKD can result from spontaneous mutations.

A number of commercial genetic testing laboratories offer gene-based testing for ARPKD. Most laboratories offer direct sequencing of the entire coding region, but the expected mutation detection rate with current technologies is only 80%. An additional 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.[4] 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,[4] and genetic testing should be largely reserved for prenatal testing and preimplantation genetic diagnosis.[1]

There are currently no specific therapies for ARPKD. Postnatal management of ARPKD infants should focus on respiratory support. Several small studies have advocated for nephrectomy to improve nutrition and enable weaning of ventilator support; however, there are no current guidelines for routine nephrectomy. Decision for nephrectomy must be made on a case-by-case basis understanding the risks of surgery and complications associated with neonatal dialysis.[4] Hypertension should be aggressively managed and may require multiple antihypertensive agents. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are considered first-line therapy.[4]

CLINICAL SUMMARY

- Renal cystic diseases encompass a broad range of disorders that manifest in both children and adults with variable clinic features.
- The identification of disease-causing genes has expanded our understanding of cystic disease pathogenesis and enhanced diagnostic accuracy.

Patients should be monitored for development of splenomegaly by abdominal examination, and annual complete blood and platelet counts should be obtained.[4] Abdominal US should be obtained at age 5, and if negative, follow-up is recommended every 2 to 3 years.[4] Cholangitis should be considered in any ARPKD patient with unexplained fever.[4]

Nephronophthisis

Disease Characteristics. NPHP (MIM 256100) is an autosomal recessive tubulointerstitial disorder and one of the most common causes of inherited end-stage kidney disease in children and young adults.[22]

The initial features typically present between 4 and 6 years of age and include polydipsia and polyuria. Decreased urinary concentration is invariably present. Slowly progressive decline in kidney function is typical of NPHP. One-third of patients develop normocytic anemia before the onset of renal insufficiency.[23,24] This early anemia may be secondary to impaired function or