

Pediatric Polycystic Kidney Disease — Ultrasound and Infant Survival Rate

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Background

Polycystic kidney disease can be diagnosed in adults and pediatric patients. It is an inherited disease that involves bilateral renal cysts without dysplasia. The condition is divided into 2 forms:

1. Autosomal recessive polycystic kidney disease, previously known as infantile polycystic kidney disease.
2. Autosomal dominant polycystic kidney disease, previously known as adult polycystic kidney disease.

Definitions

The autosomal dominant pattern occurs in adults and is the fourth common cause of renal failure in the world. It mainly affects the kidneys, heart, brain, reproductive organs, vascular smooth muscle, and small intestine.

Autosomal recessive pattern, on the other hand, affects children from perinatal age until adolescence. It affects mainly the kidneys, lungs, and liver and rarely other organs like the brain.

Epidemiology of Pediatric Polycystic Kidney Disease

Autosomal recessive (childhood) polycystic kidney disease (ARPKD) was previously labeled as 'infantile polycystic kidney disease' but discarded due to its presentation at different times in childhood.

Incidence: Varies from 1:10,000 to 1: 40,000 live births.

Prevalence: Varies from 1:600 to 1:55,000 live births.

Race and sex-related demographics:

Both forms of polycystic kidney disease affect all racial and ethnic groups and both equally affect males and females.

Etiology of Pediatric Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease is the most common inherited kidney disease in humans. It is a multi-system disorder characterized by progressive cystic dilatation of both kidneys with variable extrarenal manifestations in the gastrointestinal (GI) tract, cardiovascular system, reproductive organs, and brain.

In ARPKD, a mutation occurs on a very large gene called polycystic kidney and hepatic disease 1 gene (PKHD 1 gene). This gene is located on chromosome 6p21 which encodes a 447-kD protein called fibrocystin or polyductin. Polyductin is found to be present in the cortical and medullary collecting ducts and the thick ascending limb of the kidney, and the epithelial cells of the bile ducts. This explains varying degrees of hepatic and renal involvement.

Cyst formation is found in both ADPKD and ARPKD. Fibrocystin is responsible for the normal functioning of cilia in kidney collecting tubules; thus, any defect in this protein causes disruption in functions of renal cilia leading to cyst formation.

Genotype and phenotype correlation has been found in studies in patients with ARPKD. Truncation mutations have more severe morbidity and mortality than children born with missense or substitution mutations. Genotype testing is explained later in the diagnosis.

Pathophysiology of Pediatric Polycystic Kidney Disease

ARPKD affects mainly the kidneys and liver. Secondary involvement of other organs such as the lungs and lower extremity deformity is also seen.

Kidneys: Macroscopically, both kidneys are enlarged with the cyst formation of the collecting ducts visible as pinpoint dots on the capsular surface of the kidney. Microscopically, these cysts are around 2-3 mm in size. Marked collecting duct ectasia and interstitial edema lead to a decrease in the number of glomeruli and tubular

structures. The pelvic calyceal system and renal vessels are not affected.

The severity of the disease is directly proportional to the number of nephrons affected by the cyst. If the neonate survives and grows to the infantile stage, cysts grow larger (up to 1 cm in size) and interstitial inflammation and fibrosis occurs, which is similar to patients presenting with ADPKD.

Liver: The **classic lesion in the liver is portal fibrosis which surrounds an increased number of hyperplastic and ectatic biliary ducts.** Hepatocellular histology remains normal. Intrahepatic biliary ectasia results in the dilatation of the extrahepatic bile duct with macrocyst formation leading to an enlarged gall bladder or choledochal cysts. There is a variable degree of liver involvement in ARPKD. Severe cases manifest over time with hepatomegaly and portal hypertension present in most cases.

Symptoms of Pediatric Polycystic Kidney Disease

Renal manifestations

Classic **presentation in prenatal age is found through abdominal ultrasound.** It shows bilaterally enlarged kidneys, oligohydramnios, and the absence of fluid in the fetal bladder. Additionally, an elevation of alpha-fetoprotein in the maternal serum and meconium in the amniotic fluid may be found. Respiratory distress occurs as a sequel. If intervention is started early and aggressively, urine output improves with improvement in respiratory status which, in turn, improves renal function.

Those **infants who survive the neonatal and infantile phase have stable GFR but can develop complications in late childhood** around the age of 15. It may lead to renal insufficiency which manifests as a failure to thrive, renal osteodystrophy, anemia, polyuria, polydipsia, hyponatremia, and metabolic acidosis. Concentrating defect in the kidneys is typical in these cases. Death from renal insufficiency is not common.

Hypertension is a very common presentation in neonates, infants, and children. It is found that **hypertension is more severe in the first year of life** and, if not managed aggressively, it can lead to cardiac hypertrophy and congestive cardiac failure. Hypertension can be responsible for the majority of deaths at an early age.

Extrarenal manifestations

Pulmonary disease: Respiratory distress is present in neonates with large massive kidneys at birth due to pulmonary hypoplasia, pneumothorax or atelectasis. Severely affected infants present Potter's phenotype along with pulmonary hypoplasia. It is **characterized by deep-set eyes, flat beaked nose, low set ears, and micrognathia and joint deformities.** Death occurs soon after birth in infants with true pulmonary hypoplasia secondary to pulmonary insufficiency.

Liver disease: Manifestations of liver disease in ARPKD are evident in the form of the biliary disease and portal hypertension. These are seen in older children. Portal hypertension is **characterized by bleeding esophageal varices, hepatosplenomegaly along with hypersplenism picture of anemia, leukopenia, and thrombocytopenia in blood work.** Liver function tests show normal results. The biliary disease presents itself in the form of choledochal cysts. Complicated/severe cases present with cholangitis or cholelithiasis which leads to sepsis. If prenatal transplantation is performed, hepatic complications dominate the clinical presentation of ARPKD.

Diagnosis of Pediatric Polycystic Kidney Disease

Ultrasonography

Kidney: USG findings in ARPKD can be found as early as at 24 weeks of gestation in the prenatal

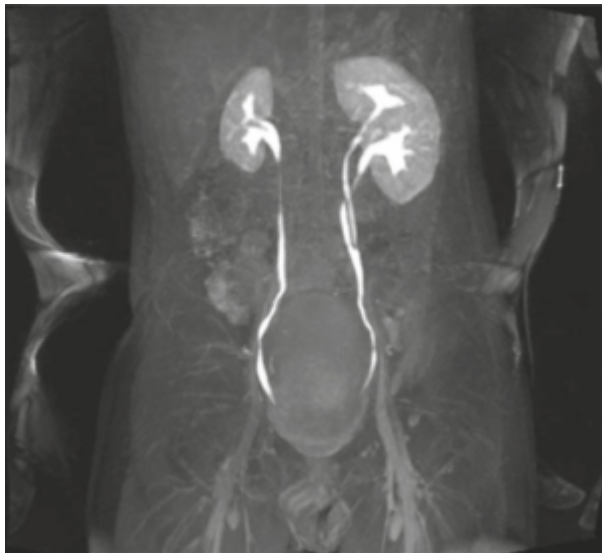


Image: "Duplication of pelvis and ureter on the left side. Hypoplastic right kidney with vesico-ureteral reflux, grade III." by Vegar-Zubovic S, Kristic S, Lincender L. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

period. **Characteristic findings include bilaterally enlarged kidneys, oligohydramnios, and the absence of urine in the bladder**, although false positive and false negative tests have been reported. Maternal alpha-fetoprotein may be elevated. Post-natal ultrasound shows bilaterally enlarged kidneys which are diffusely echogenic with poor corticomedullary differentiation.

The presence of the hypoechoic subcapsular rim of parenchyma is very specific in these cases. Macrocysts are seen but are less than 2 cm in diameter. The **kidneys in ARPKD decrease in size as the infant grows**. This is the main differentiating feature from autosomal dominant polycystic kidney disease where kidneys enlarge in size with age.

Liver: USG shows massive hepatosplenomegaly with the hyperechoic liver. There is dilatation of the peripheral intrahepatic ducts and the main bile ducts. Choledochal cysts are found in some cases, but hepatic cysts are not commonly seen.

CT/MRI scan

CT/MRI scans are performed to aid the diagnosis of ARPKD in case USG findings are equivocal. Magnetic resonance imaging (MRI) shows enlarged kidneys with microcystic dilatation of collecting ducts which are filled with water. MRI of the liver also shows characteristic findings of bile duct ectasia and portal vein fibrosis. The CT scan shows enlarged kidneys with radial or linear opacification in the cortex and the medulla.

Molecular genetic testing

Molecular genetic testing is done only when the diagnosis remains unclear, in assisting prenatal diagnosis and for genetic counseling to identify carriers of

mutations of the PKHD1 gene. Genetic testing includes the following tests:

- Mutation scan
- Gene sequencing analysis
- Targeted mutation analysis
- Linkage analysis
- Deletion and duplication analysis

Differential Diagnosis of Pediatric Polycystic Kidney Disease

- Multiple benign simple cysts of the kidneys
- Tuberous sclerosis
- von Hippel-Lindau syndrome
- Medullary sponge kidney
- Medullary cystic kidney disease
- Autosomal dominant polycystic kidney disease
- Renal dysplasia
- Meckel syndrome
- Congenital hypernephronic nephromegaly with tubular dysgenesis
- Bilateral parapelvic cysts

Management and Treatment of Pediatric Polycystic Kidney Disease

Currently, treatment is only supportive.

Neonates who present with respiratory distress require mechanical ventilation.

Management of patients suffering from ARPKD not only involves the patient but the whole family. Psychosocial support by social workers and psychologists play a vital role in improving their prognosis.

Medical management encompasses a multidisciplinary approach with pediatric nephrologists, cardiologists, hepatologists, neonatologists, geneticists, nurses with intensive care skills, dieticians and social workers which provide optimal comprehensive care for affected children and their families.

Survival rates of children suffering from ARPKD are increasing with the advent of neonatal intensive care and artificial ventilation. Complicated cases require bilateral nephrectomy along with peritoneal dialysis to allow optimal ventilation.

Poor feeding is common in infants with ARPKD due to gastric compression by enlarged kidneys. The **infants may require supplemental nasogastric feeding to prevent growth impairment due to poor nutrition.**

Sodium bicarbonate is given to curb metabolic acidosis.

Polyuria is treated with thiazide diuretics which act on distal collecting tubule and decreases water delivery.

Diuretics such as furosemide and hydrochlorothiazide are used to treat edema due to renal disease.

Hypertension is treated with beta-blockers, ACE inhibitors, calcium channel blockers and

diuretics. These drugs are effective in cases presenting with congestive cardiac failure.

Angiotensin-converting enzyme inhibitors have also been effective in certain hypertensive cases of ARPKD.

Chronic kidney disease manifesting in renal osteodystrophy and anemia is aggressively treated with growth hormones and nutritional supplements for better prognosis.

End-stage renal disease is treated with renal transplantation and/or peritoneal dialysis. This is evident from growth failure with progressive uremia. Peritoneal dialysis is very effective in neonates, where enlarged kidneys compromise the patient's respiratory function. This treatment is even successful in children with hepatomegaly, splenomegaly associated with bilaterally enlarged kidneys.

A kidney transplant is most effective in children presenting with renal insufficiency. During the procedure, a bilateral nephrectomy is also performed to treat uncontrolled hypertension or to replace massively enlarged kidneys. Successful kidney transplantations have very good prognoses in children which is evident in the form of their growth and development milestone increase.

Portal hypertension can be treated by inserting an esophageal endoscopy for sclerotherapy or banding of esophageal varices. In refractory cases of severe portal hypertension, a choice of portacaval shunting or liver transplantation is considered. UTI and sepsis resulting from bacterial cholangitis are treated with the appropriate antibiotic therapy advised by the blood culture.

Complications

- Failure to thrive - the child does not put on weight at the expected rate. Children with autosomal recessive polycystic kidney disease (ARPKD) will fail to thrive after birth. The reasons for this are uncertain.
- Hypertension.
- Children with ARPKD have an increased risk of developing a urinary tract infection (UTI).
- Hematuria is commonly seen in ADPKD

Progress and Prognosis of Pediatric Polycystic Kidney Disease

The prognosis of ARPKD is dependent on the severity and age at presentation.

The mortality rate is high in patients presenting in perinatal and neonatal age groups with severe renal diseases like those who require ventilation, those with hypertension and those who are diagnosed to be in end-stage renal disease.

Long-term survival of the patient is found to be better once earlier years have been survived. In a study of 254 cohorts of ARPKD patients from North America, neonatal survivors reported 1 and 5-year patient survival rates of 85 % and 82 % respectively, while renal survival at 5, 10 and 20 years of 86 %, 71 % and 42 % respectively.

Note: With increasing advancement in medical treatment and the management of end-stage renal disease, long-term survival rates are further predicted to rise.

Review Questions

1. Autosomal recessive polycystic kidney disease affects all parts of the kidney except:

- A. Glomeruli
- B. Tubules
- C. Pelvicalyceal system
- D. Renal vessels
- E. Pelvicalyceal system and renal vessels

2. Cardiac manifestations of ARPKD include:

- A. Hypertension
- B. Cardiac hypertrophy
- C. Congestive cardiac failure
- D. All of the above

3. A newborn is found to be in respiratory distress with RR of 50 breaths per minute and blood pressure of 180/110 mm Hg. The neonatologist gently examined the abdomen before preparing for artificial ventilation. He found a bilateral mass in the paravertebral lumbar areas. In the meantime, one of the nurses suggested that her previous sibling suffered the same symptoms and genotype testing was suggestive of mutations of the PKHD1 gene (polycystic kidney and hepatic disease 1). What of the following is the likely diagnosis of this neonate in respiratory distress?

- A. Autosomal dominant polycystic kidney disease
- B. Autosomal recessive polycystic kidney disease
- C. Medullary cystic kidney disease
- D. von Hippel Lindau syndrome

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<http://emedicine.medscape.com/article/983281-overview>

Correct answers: 1E; 2D; 3B

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