Autosomal Recessive Polycystic Kidney Disease

Synonyms: infantile polycystic kidneys, polycystic kidney and hepatic disease type I

**Note:** the names of infantile and adult polycystic kidney disease (PKD) are no longer used because they are not an accurate description. Both autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) can involve the presence of renal cysts at any time during an affected person's life, from the prenatal period to adolescence or older.

ARPKD is the most common genetic cystic renal disease occurring in infancy and childhood. However, it is nonetheless a rare disorder and is much less common than ADPKD. It is an autosomal recessive disorder due to mutation of the number 6 chromosome at gene map locus 6p21.1-p12, a gene encoding fibrocystin.\(^1\)

A single gene defect leads to differing degrees of renal and hepatic involvement, with very different phenotypes and clinical outcome within even one affected family.\(^2\) Kidneys are bilaterally enlarged and contain large numbers of cysts throughout the organ, due to the dilatation and elongation of renal collecting ducts. At birth, the interstitium and the rest of the tubules are normal but they may later develop interstitial fibrosis and tubular atrophy that can cause end-stage kidney disease. There may be hepatic as well as renal involvement:

- Hepatic involvement with bile duct ectasia is sometimes called Caroli's disease.
- Generally, the later the manifestation of the renal disease, the more marked the liver disease. The renal and hepatic disease tend to show opposite degrees of severity
- Severe cases of liver disease may progress to cirrhosis with portal hypertension and oesophageal varices.

**Epidemiology**

Studies suggest a prevalence of between 5-10 in 100,000 births (with carrier frequency of between 1 in 50-70).\(^3\)

**Presentation**

The presentation of the disease can be highly variable, even within the same family. There are a number of classifications but this is the one that is used most often and is based on age at presentation which is, in turn, related to disease severity.\(^3\)

- **Category 1** presents perinatally:
  - Infants are born with a very large abdomen due to massive renal enlargement and this may complicate delivery. About 90% of the collecting ducts are dilated but the liver is scarcely involved.
  - Severe renal impairment in utero produces oligohydramnios and subsequent pulmonary hypoplasia. Other clinical findings resulting from oligohydramnios include Potter's facies (flattened nose, micrognathia and large, floppy, low-set ears) and club foot.
  - Approximately 75% of cases result in the death of the baby within a week of birth.

- **Category 2** presents neonatally:
  - Infants have palpable kidneys at birth.
  - About 60% of the kidney is affected and there is mild liver disease.
  - As renal impairment is often less severe in utero there is less risk of pulmonary hypoplasia but the kidney disease is progressive, usually causing death within a few months.
• **Category 3** presents in *infancy*:
  - This tends to present when babies are a few months old.
  - Approximately 25% of renal collecting ducts are dilated, with moderate hepatic periportal fibrosis.
  - There are enlarged kidneys and hepatosplenomegaly on examination.
  - Affected babies and children often develop chronic kidney disease with or without portal and systemic hypertension.
  - The principle cause of mortality is end-stage kidney disease, usually in adolescence.

• **Category 4** presents in *childhood*:
  - There is marked liver disease.
  - Fewer than 10% develop end-stage kidney disease.
  - The disease usually presents between 6 months and 5 years.
  - There is variable renal enlargement and hepatosplenomegaly.
  - Significant liver involvement results in portal hypertension.
  - Morbidity and mortality are usually due to portal hypertension, including variceal bleeding and thrombocytopenia or anaemia from hypersplenism.
  - Mortality is the lowest of the four categories, with around 80% surviving beyond the age of 15 years.

### Differential diagnosis

Distinguish from other causes of renal and hepatic cystic disease and other conditions causing enlargement of the kidneys:

- ADPKD.
- Multicystic dysplasia.
- Bardet-Biedl syndrome (a ciliopathy causing multivisceral abnormalities, including polycystic kidneys).[^4]
- Meckel-Gruber syndrome.
- Hydronephrosis.
- Wilms' tumour.
- Renal vein thrombosis.

### Investigations[^5]

- **Ultrasound:**
  - It is the imaging tool of choice in the perinatal period. With the increased use of routine scanning, approximately 50% of cases are now diagnosed prenatally. Large kidneys may appear 'bright' from about 13 weeks and, between 20-30 weeks, oligohydramnios may be detectable.
  - Prenatal diagnosis is unlikely before the second half of pregnancy unless there are strong reasons to suspect the condition, such as an affected older child. Early ultrasound is not very reliable at detecting the condition.

- In older children, CT and MRI scanning may be used to monitor liver disease:
  - Magnetic resonance cholangiography to assess the liver.
  - CT scanning may also show renal calcification that is missed on plain film.

- **Plain X-ray:**
  - Large kidneys and even medial displacement of the bowel are usually visible on AXR.
  - Enlarged liver or spleen may also be seen.
  - In Potter's syndrome, a CXR may show hypoplastic lungs with pneumothorax and elevated diaphragm.

- **Intravenous urography:**
  - This may be used in the older child but the contrast material is nephrotoxic in renal inadequacy.
Blood and urine investigations:
- These are useful in evaluating and monitoring patients with ARPKD but none is diagnostic. Although normal initially, LFTs are often abnormal in the later stages of the disease.

Genetic testing in ARPKD:
- This can be performed using linkage analysis where the patient's family has at least one diagnosed index case. Where this is not possible, direct genetic testing is improving. However, it is not yet offered for amniocentesis or diagnosis.

Prenatal and pre-implantation diagnosis
- There may be suspicion if there is a family history of the disease but ultrasound, even into the second trimester, is unreliable in many cases.
- Late suspicion may arise from clinical detection of oligohydramnios or noting a large abdomen on routine late scan.
- Where ultrasound is uncertain, MRI can be a useful adjunct.
- When counselling parents, it is important to stress that diagnostic tests are unreliable in this highly variable condition.

Due to the poor prognosis that can be associated with the disease, there is a demand for prenatal diagnosis. Pre-implantation genetic diagnosis can provide an alternative without the trauma of a termination in the case of an affected fetus.

Management

Survival of neonates depends on the degree of pulmonary hypoplasia and the skill of the neonatal intensive care unit.

- Very large kidneys may press on the diaphragm and impede ventilation.
- To facilitate ventilation, nephrectomy may be necessary.
- Fluid overload can be managed with diuretics and continuous renal replacement therapy.
- Hypertension occurs in the majority of children and can be severe; it should be aggressively treated with angiotensin-converting enzyme (ACE) inhibitors.
- Urinary tract infections will require antibiotics.
- The presence of chronic kidney disease will require:
  - Treatment of anaemia with iron and erythropoietin.
  - Prevention of metabolic bone disease with calcium supplements, phosphate binders, and parathyroid-suppressing medication.
  - Growth hormone to counter the growth-limiting effects of uraemia.
- End-stage kidney disease requires dialysis or transplantation.
- Hepatic complications will also require treatment - eg, sclerotherapy for varices or the use of portocaval and splenorenal shunts.
- Combined liver and renal transplant may be considered.

Primary care pointers:

- Between a quarter and a third of ARPKD children fail to thrive after birth; the reason for this is unknown. Supplemental feeding may be required.
- Many affected children have polyuria and polydipsia. They often encounter problems with bedwetting.
- ARPKD children are more prone to dehydration with fever, vomiting or diarrhoea; fluid intake should be adjusted with weather and activity.

Apart from complications resulting from renal and liver disease, intracranial aneurysms have been reported.
Prognosis

In those with pulmonary hypoplasia the outlook is very poor and even ventilation is unlikely to save lives.

- There is a high mortality rate in the first month of life while the clinical spectrum of surviving patients is much more variable. [8]
- If the neonatal period is survived, the prognosis is much better but there must be ongoing attention not just to renal function but to the management of systemic and portal hypertension.
- Disease progression may have organ-specific patterns.
- Only a subset of patients may be at risk for developing clinically significant manifestations of periportal fibrosis. [8]

The first study reporting the long-term outcome of ARPKD patients with defined PKHD1 mutations found that:

- The 1- and 10-year survival rates were 85% and 82% respectively.
- Chronic kidney disease was first detected at a mean age of 4 years.
- Renal survival rates, where the end point is defined as start of dialysis/renal transplantation or by death due to end-stage kidney disease, were 86% at 5 years, 71% at 10 years and 42% at 20 years. [9]

Those who survive to adulthood still see progressive deterioration of renal function and risk of hepatic complications.

Further reading & references


1. Polycystic Kidney Disease, Autosomal Recessive, ARPKD: Online Mendelian Inheritance in Man (OMIM)

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