Polycystic Kidney Disease: Autosomal Recessive Type

Contents

Autosomal recessive polycystic kidney disease (ARPKD) or polycystic kidney and hepatic disease 1 (*PKHD1*) is an often devastating form of polycystic kidney disease. It is also known as infantile polycystic kidney disease. The incidence of ARPKD is estimated to be 1 in 20,000 live births, and the frequency of the heterozygous carrier state is 1 in 70 (Lonergan et al. 2000).

Synonyms and Related Disorders

Congenital hepatic fibrosis (Caroli disease); Infantile polycystic kidney disease; Polycystic kidney and hepatic disease

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. No clear evidence of genetic heterogeneity.
3. ARPKD: a hepatorenal fibrocystic disorder with pleiotropic effects (Hartung and Guay-Woodford 2014).
4. Molecular cause (Harris and Rossetti 2004):
   1. Mutations in the *PKHD1* gene on chromosome 6p21.1-p12 (Zerres et al. 1994), encoding a putative receptor protein, fibrocystin (or polyductin)
   2. The ARPKD protein, fibrocystin, is predicted to be an integral membrane, receptor-like protein containing multiple copies of an Ig-like domain (TIG).
   3. Fibrocystin is localized to the branching ureteric bud, collecting and biliary ducts, consistent with the disease phenotype and often absent from ARPKD tissue.
   4. In common with other PKD-related proteins, fibrocystin is localized to the primary cilia of renal epithelial cells, reinforcing the link between ciliary dysfunction and cyst development.
   5. The majority of patients are compound heterozygotes, and preliminary genotype/phenotype studies associate two truncating mutations with severe disease.
   6. The complexities of *PKHD1*, marked allelic heterogeneity, and high level of missense changes complicate gene-based diagnostics.
5. Genotype-phenotype correlations (Denamur et al. 2010):
   1. All patients carrying two truncating mutations displayed a severe phenotype with

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perinatal or neonatal demise (Bergmann et al. 2003; Dell and Avner 2011).
2. Patients who survive have at least one missense mutation.

6. The next challenges will be to determine how various factors, such as specific mutations in the *PKHD1* gene, variations in modifying gene loci, modulation by as yet unspecified environmental factors, or gene-environment interactions, contribute to the marked variability in survival and disease expression observed among ARPKD patients (Guay-Woodford and Desmond 2003).

Clinical Features

1. The most common heritable cystic renal disease manifesting in infancy and childhood (Lonergan et al. 2000).
2. A wide variable clinical spectrum (Zerres et al. 2003; Adeva et al. 2006), ranging from severe renal impairment, and a high mortality rate in infancy to older children and adolescents with minimal renal disease and complications of congenital hepatic fibrosis, cholangitis, and portal hypertension.
3. Principal manifestations:
   1. Fusiform dilatation of renal collecting ducts and distal tubuli
   2. Dysgenesis of the hepatic portal triad
4. Clinical characteristics at presentation: variable clinical spectrum:
   1. Zero to 1 month:
      1. Prenatal diagnosis made
      2. Positive family history
      3. Pneumothorax
      4. Flank mass
      5. Hypertension
      6. Renal insufficiency
   2. >1 month–1 year:
      1. Frank mass
      2. Hepatomegaly
      3. Hypertension
      4. Urinary tract infection
   3. >1–5 years:
      1. Hepatomegaly
      2. Portal hypertension
   4. >5 years:
      1. Hepatomegaly
      2. Hypertension
      3. Renal insufficiency
      4. Portal hypertension
   5. Predominance of renal abnormalities in younger children.
   6. Predominance of hepatic disease in older children and adolescents.
   7. Tendency of inverse relative degrees of kidney and liver involvement:
      1. Children with severe renal disease usually with milder hepatic disease
      2. Children with severe hepatic disease with milder renal impairment
   8. ARPKD may be underdiagnosed in adulthood because the sonographic data are not specific. Moreover, a correlation between age and hepatic involvement is not always seen, so this disease must be suspected when portal hypertension is present in a young adult with renal failure (Pérez et al. 1998).
5. "Potter" phenotype developed in affected fetuses:
   1. Pulmonary hypoplasia, often incompatible with life
   2. Characteristic face:
      1. Short and snubbed nose
      2. Deep eye creases
      3. Micrognathia
      4. Low-set flattened ears
   3. Deformities of the spine and limbs (clubfoot)
6. Renal manifestations:
   1. Frequent loss of concentrating ability of the kidney
   2. Common recurrent urinary tract infections
   3. Proteinuria
   4. Hematuria
   5. Creatinine clearance improving early but declining progressively during adolescence
   6. Hypertension early in life but usually regresses
   7. Enlarged kidneys
   8. End-stage renal disease

7. Hepatic manifestations:
    1. Congenital hepatic fibrosis (Lieberman et al. 1971):
        1. Invariably present but only occasionally do hepatic symptoms predominate.
        2. Two predominant features characterizing the liver in ARPKD:
            1. Bile ducts: abnormally/irregularly formed, often increased in number, and dilated intrahepatic bile ducts
            2. Portal tracts: enlarged and fibrotic
        3. Normal hepatic parenchyma.
        4. Hepatocellular function almost always normal in affected patients, even when they have relatively severe portal tract disease.
        5. Not by itself a diagnostic (not pathognomonic) sign. Congenital hepatic fibrosis has been observed in the following situations (Lonergan et al. 2000):
            1. Meckel-Gruber syndrome
            2. Vaginal atresia
            3. Tuberous sclerosis
            4. Juvenile nephronophthisis
            5. Rarely autosomal dominant polycystic kidney disease
    2. Caroli disease:
        1. Congenital hepatic fibrosis accompanied by a nonobstructive dilation of the intrahepatic bile ducts
        2. Clinical risk of secondary complications:
            1. Stone formation
            2. Recurrent cholangitis: may result from ectatic bile ducts
            3. Hepatic abscesses
            4. Rare cholangiocarcinoma
    3. Hepatomegaly
    4. Portal hypertension (Lonergan et al. 2000):
        1. The most common sequelae of congenital hepatic fibrosis
        2. Splenomegaly
        3. Variceal bleeding
        4. Hypersplenism:
            1. Leukopenia
            2. Thrombocytopenia
            3. Anemia
            4. Increased susceptibility to infections resulting from leukopenia associated with splenic sequestration
    5. Ascending cholangitis (Lonergan et al. 2000):
        1. Presumably caused by entry of nonsterile gastrointestinal contents into the dilated intrahepatic bile ducts
        2. Common in patients with macroscopically dilated bile ducts
        3. Clinical features:
            1. Abdominal pain
            2. Fever
            3. Elevation in levels of hepatic enzymes
        4. Tends to recur
        5. May lead to hepatic abscess formation, sepsis, and death
8. Cerebral aneurysm, a common feature of ADPKD, reported in an adult with ARPKD
9. Prognosis:
    1. Thirty to fifty percent of affected neonates die shortly after birth in respiratory insufficiency due to pulmonary hypoplasia.
    2. Most neonates without severe pulmonary hypoplasia will survive (Sumfest et al. 1993).
    3. Recent trend with improved prognosis.
    4. Sixty-seven percent of children who survive the newborn period with life-sustaining renal function at 15 years of age.

Diagnostic Investigations

1. Radiography in neonates and infants with moderate to severe renal disease:
    1. Smoothly enlarged kidneys because of the numerous dilated collecting ducts
    2. Abdominal distension
    3. Gas-filled bowel loops often deviated centrally
    4. Pulmonary hypoplasia and small thorax in the baby with severe kidney disease
    5. Pneumothorax common at birth following assisted ventilation
2. Ultrasonography:
    1. The absence of renal cysts in both parents as demonstrated by ultrasound examination

2. Neonatal ultrasonography with more marked renal cystic disease:
    1. Massive enlarged kidneys
    2. Increased echogenicity of the entire parenchyma
    3. Loss of corticomedullary differentiation
    4. Loss of central echo complex
    5. Small macrocysts (unusual focal rosettes consisting of a cluster of the radially oriented, dilated collecting tubules) (Stein-Wexler and Jain 2003)
    6. Usually small bladder
    7. Increased hepatic echogenicity, mainly in medulla
3. Ultrasonography in children with more prominent hepatic fibrosis:
    1. Massive kidney enlargement
    2. Increased hepatic echogenicity, mainly in medulla
    3. Macrocysts:
        1. Less than 2 cm in diameter
        2. Tend to become larger and more numerous over time
    4. Enlarged echogenic liver
    5. Hepatic cysts
    6. Pancreatic cysts
    7. Splenomegaly secondary to portal hypertension
    8. Hepatofugal-flow duplex and color-flow Doppler

3. CT scan:
    1. Nonenhanced CT: smooth, enlarged, and low-attenuating kidneys, likely the reflection of the large fluid volume in the dilated ducts
    2. CT with contrast:
        1. Kidneys with a striated pattern representing accumulation of contrast material in the dilated tubules
        2. Linear opacifications representing retention of contrast medium in dilated medullary collecting ducts
        3. Macrocysts appearing as well-circumscribed rounded lucent defects
        4. Time of delay in visualizing the contrast medium in the kidneys, proportionate to the severity of renal impairment
4. Ultrasonography and magnetic resonance cholangiography to investigate the presence of an extent of Caroli disease in children with autosomal recessive polycystic kidney disease
5. MRI of affected children (perinatal, neonatal, and infantile course) (Kern et al. 1999):
    1. Kidney appearance:
        1. Enlarged, humpy but still reniform in shape
        2. Homogeneously grainy parenchyma
    2. Signal intensity:
        1. Hypointense on T1-W spin-echo sequences
        2. Hyperintense on T2-W turbo spin-echo sequences
    3. Rapid acquisition with relaxation enhancement (RARE)-MR urography:
        1. Hyperintense, linear radial pattern seen in the cortex and medulla representing the characteristic microcystic dilatation of collecting ducts
        2. Possible few circumscribed small subcapsular cysts
    4. MR cholangiography: a valuable method to establish the diagnosis and demonstrate the extent of Caroli disease by showing the entire biliary free from different angles (Jung et al. 1999)
6. Histopathology of the kidney and liver (Sherwani et al. 2010):
    1. Kidneys: Grossly enlarged with multiple cysts on the external surface that involve the cortex and medulla and are located in collecting ducts and tubules, lined by cuboidal epithelium.
    2. Liver:
        1. Grossly, cysts are also present in an enlarged liver where they form due to enlarged portal areas forming anastomosing channels, with the biliary structures forming dilated sacs.
        2. Hepatic fibrosis is an essential diagnostic criterion for this autosomal recessive disease.
    3. The involvement of the renal collecting system and hepatic ductal plate malformation is due to the failure of terminal

differentiation of the collecting duct and biliary systems, causing oligohydramnios leading to pulmonary hypoplasia which is the cause of morbidity, in 30% of cases.

7. Molecular diagnosis:
    1. Linkage analysis of the affected family using 6p21 markers demonstrating linkage to the *ARPKD1* gene with the affected proband.
    2. 33 different mutations detected on 57 alleles (Rossetti et al. 2003):
        1. 51.1% in ARPKD
        2. 32.1% in congenital hepatic fibrosis/Caroli disease
        3. Two frequent truncating mutations:
            1. 9689delA (9 alleles)
            2. 589insA (8 alleles)
        4. Mutation detection rate:
            1. High in severely affected patients (85%)
            2. Lower in moderate severe ARPKD (41.9%)
            3. Low, but significant, in adults with congenital hepatic fibrosis/Caroli disease (323.1%)
        5. Complications for the prospects for gene-based diagnostics:
            1. Large gene size
            2. Marked allelic heterogeneity
            3. Clinical diversity of the ARPKD phenotype
    3. Direct DNA analysis – available clinically:
        1. Mutation scanning
        2. Sequence analysis
        3. Targeted mutation analysis
        4. Deletion/duplication analysis
        5. Linkage analysis
    4. Next-generation sequencing of the PKHD1 gene is a very useful method of molecular diagnosis in patients with a full clinical picture of ARPKD, and it has a high detection rate. Furthermore, its relatively low costs and rapidity allow the molecular genetic analysis of patients without the full clinical criteria of ARPKD, who might also have mutations in the PKHD1 gene (Obeidova et al. 2015). The estimated costs and the time invested for molecular screening of genes with large size and allelic heterogeneity such as PKHD1 demand the use of next-generation sequencing (NGS) technologies for a fast, accurate, and cost-effective molecular diagnostic tool for identifying mutations in targeted genes sequence analysis (Edrees et al. 2016; Melchionda et al. 2016).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: 25%
    2. Patient's offspring: not increased (theoretical risk 0.7%)
2. Prenatal diagnosis:
    1. Ultrasonography in most severely affected fetuses:
        1. Enlarged, echogenic kidneys (main US signs of ARPKD) (Zerres et al. 1988)
        2. Dilated collecting ducts
        3. Characteristic hepatic ductal plate malformation
        4. A small or nonvisualized bladder
        5. Oligohydramnios attributable to poor fetal renal output
        6. Unreliable especially in early pregnancy
    2. Molecular genetic testing by mutation scanning of *PKHD1* is available clinically by analysis of fetal DNA obtained by amniocentesis or CVS. Both disease-causing alleles of an affected family member must be identified, or linkage has been established in the family before prenatal testing can be performed. The ARPKD locus mapped to proximal chromosome 6p allowing haplotype-based prenatal diagnosis in "at-risk" family with a previously affected child in whom prior family studies have identified informative linked markers (Zerres et al. 1998a). An absolute prerequisite for these studies is an accurate diagnosis of ARPKD in the previously affected sib (Zerres et al. 1998b; Dell 2011).
    3. Preimplantation genetic diagnosis may be available for families in which the disease-

causing mutations have been identified (Sweeney and Avner 2014).

3. Management (Dell 2011):
    1. Initial management of affected infants to focus on stabilization of respiratory function. Mechanical ventilation may be necessary to treat both pulmonary hypoplasia and respiratory compromise from massively enlarged kidneys.
    2. Water and electrolyte balance.
    3. Peritoneal dialysis may be required for neonates with oliguria or anuria within the first days of life.
    4. Vigorous treatment of systemic hypertension with antihypertensive agents:
        1. ACE inhibitors
        2. Calcium channel blockers
        3. Beta blockers
        4. Judicious use of diuretics (e.g., thiazides, loop diuretics)
    5. Importance of early detection and appropriate management of systemic and portal hypertension (Roy et al. 1997).
    6. Antibiotics for treatment of urinary tract infections.
    7. Management of renal osteodystrophy in children with ARPKD and chronic renal insufficiency:
        1. Calcium supplements
        2. Phosphate binders
        3. 1,25-Dihydroxyvitamin D3 to suppress parathyroid hormone (PTH)
        4. Erythropoietin (EPO):
            1. Increases hemoglobin levels
            2. Improves the overall well-being of the child
    8. Potential use of recombinant human growth hormone therapy to improve the growth of children with uremia (Lilova et al. 2003).
    9. Therapeutic options available for the treatment of portal hypertension in children (Lonergan et al. 2000):
        1. Conservative management
        2. Control of variceal bleeding:
            1. Sclerotherapy effective in controlling bleeding
            2. Banding of varices
            3. Placement of portosystemic shunts occasionally necessary to reduce bleeding and the formation of additional varices
        3. Prompt management with antibiotics and, when indicated, surgical drainage to help reduce morbidity and mortality associated with ascending cholangitis
        4. Splenectomy for hypersplenism
        5. Liver transplantation in patients with severe hepatic dysfunction or chronic cholangitis
    10. Replacement therapy for renal failure:
        1. Renal dialysis
        2. Renal transplant
    11. Kidney transplantation (Jamil et al. 1999):
        1. Liver disease did not progress rapidly after initiation of renal replacement therapy and did not subsequently present a clinical problem.
        2. When it occurs, recurrent bleeding appears to be controllable with sclerotherapy.
        3. Cholangitis is not a significant problem.
        4. Renal transplantation is appropriate for patients with ARPKD and that prophylactic portacaval shunting or combined liver/kidney transplantation is unnecessary.

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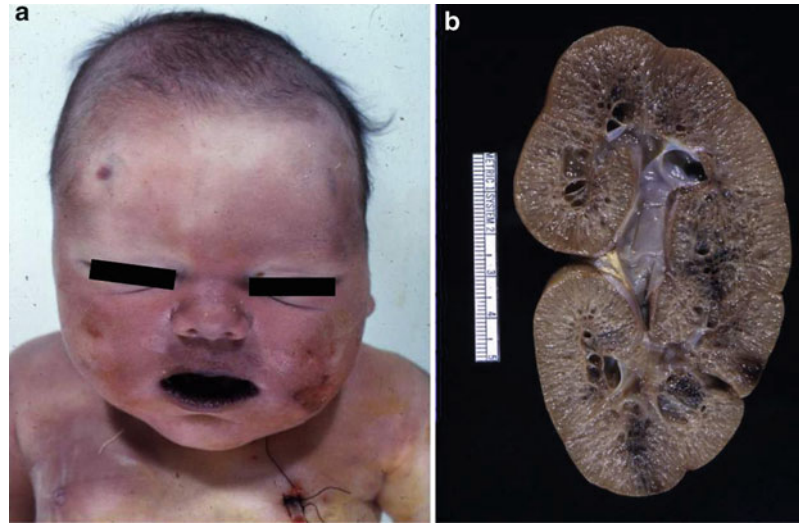

Fig. 1 A newborn with ARPKD showing Potter facies (**a**). The spongy appearing cut surface of a kidney from the same patient is due to generalized dilatation of the collecting ducts in both cortex and medulla (**b**)

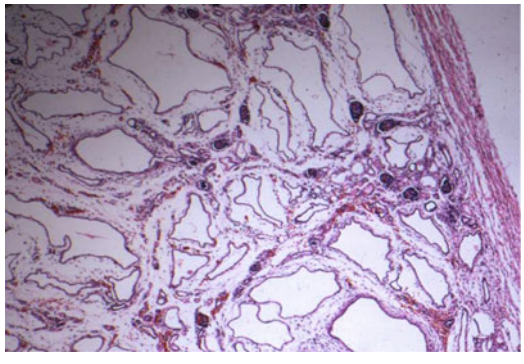

Fig. 2 Photomicrograph of a kidney of a neonate (37 weeks gestation) with ARPKD showing markedly dilated collecting ducts in the medulla (*top*) and the cortex (*bottom*). The infant also had intrahepatic bile duct proliferation and mild cystic changes and pulmonary hypoplasia

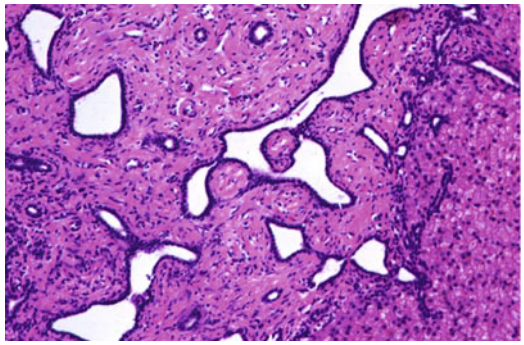

Fig. 3 Photomicrograph of the liver of a 2-year-old girl with congenital hepatic fibrosis, consistent with ARPKD. Note the irregularly dilated branching bile ducts. There is abundant fibrous connective tissue in this enlarged portal tract

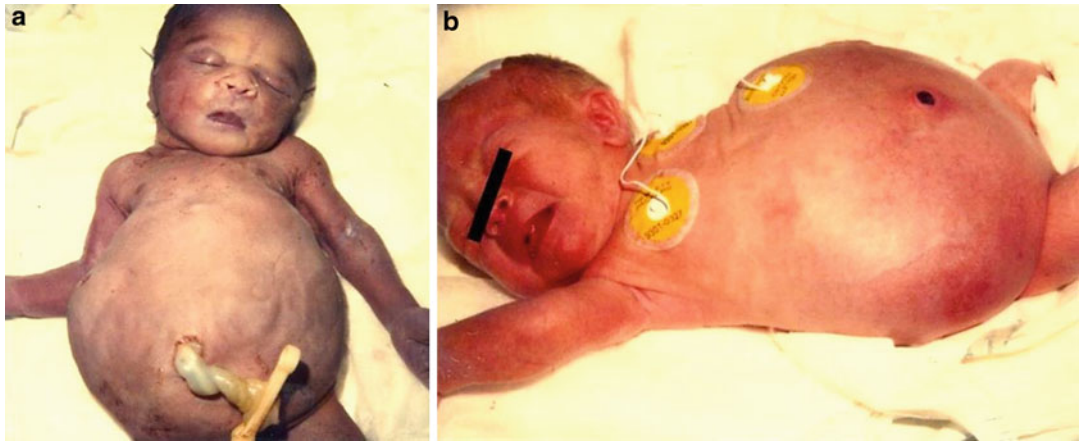

Fig. 4 Two neonates (**a**, **b**) with ARPKD showing markedly distended abdomen

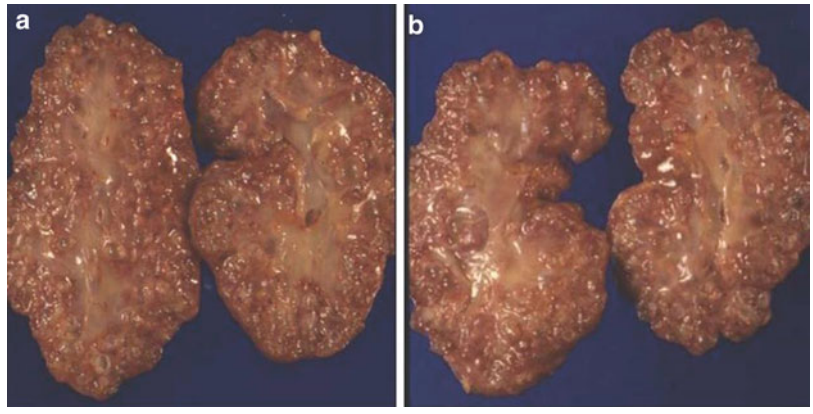

Fig. 5 (**a**, **b**) Kidneys in another neonates with ARPKD