

Autosomal recessive polycystic kidney disease

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Abstract

Recessive type or infantile polycystic kidney disease is an inherited disorder with cystic dilatations of the collecting ducts frequently associated with hepatic involvement, consisting of biliary dysgenesis and periportal fibrosis . The gene responsible for the disease, PKHD1, located on the short arm of chromosome 6, has recently been identified. It contains more than 80 exons and codes for a protein called fibrocystin or polyductin. ARPKD is a rare disease that affects 1/40,000 children/year. Prenatal ultrasonography shows hyperechogenic, enlarged kidneys and, in the more severe forms, oligohydramnios. After birth, in addition to nephromegaly, hypertension is common and often severe, and urinary tract infection may occur. Ultrasonography shows hyperechogenic, enlarged kidneys, sometimes with small cysts. Intravenous urography visualization of contrast medium in the collecting tubules is prolonged (> 24 h). On renal biopsy, cystic dilations of the collecting tubules are observed. Renal failure rarely occurs before 15 years of age. Liver involvement is always present and may be the predominant clinical feature with portal hypertension and/or acute bacterial cholangitis. Liver function remains normal. Ultrasonography reveals dilatation of the peripheral intrahepatic ducts and the main bile ducts. Liver involvement is also called congenital hepatic fibrosis.

Keywords

Autosomal recessive polycystic kidney disease (ARPKD), ultrasonography, hyperechogenic kidneys, chromosome 6p21.

Disease name and synonyms

Autosomal recessive polycystic kidney disease (ARPKD)

Polycystic kidney disease, recessive type

Definition

The term polycystic kidney disease should be reserved for two hereditary diseases: autosomal recessive polycystic kidney disease (ARPKD)

and, less commonly, autosomal dominant polycystic kidney disease (ADPKD).

ARPKD typically presents in infancy, although there are childhood and adolescent forms which are generally less severe [1,2]. ARPKD is characterized by cystic dilatations of renal collecting ducts with hepatic abnormalities consisting of bile duct dysgenesis and periportal fibrosis.

Prevalence

The estimated incidence of ARPKD is 1/10,000 to 1/40,000 children/year [2,3].

Clinical description

There are several modes of presentation depending on the age of onset and the predominance of hepatic or renal involvement. Although different genetic abnormalities have been proposed [4], familial studies have shown that a single genetic defect can lead to varying degrees of renal and hepatic involvement [1,5-7]. In one family, for example, three affected fetuses had different outcomes [5]. Recognition of this variability in disease expression is a potentially important consideration for parents with an affected fetus who are contemplating termination of the pregnancy.

The development of antenatal ultrasonography has enhanced our understanding of the natural history of this disease. Severe cases can be detected after 24 weeks of gestation by antenatal ultrasonography which shows markedly enlarged kidneys with increased echogenicity but no visible cysts [3,8]. These changes may be accompanied by oligohydramnios and the absence of urine in the bladder. These infants usually die early from pulmonary insufficiency secondary to pulmonary hypoplasia, with or without Potter's syndrome; if, however, pulmonary function can be improved, the urine output often increases with a concurrent improvement of renal function [1].

Less severe cases may not be detected by antenatal ultrasonography. The kidneys increase in size after birth, causing marked abdominal distention. A few years later, however, the kidneys may no longer be enlarged (*via* an uncertain mechanism that may be related in part to fibrosis) [9,10]. This period of regression is followed by gradual renal enlargement.

Those children who survive the first month have as much as an 80% chance of living to more than 15 years of age [1]. However, they tend to show a progressive increase of clinical manifestations of renal dysfunction including [10-13]:

- hyponatremia during the first few weeks of life due to impaired diluting capacity;

- poor concentrating ability in all patients with a maximal urine osmolality below 500 mosmol/kg;
- low urinary acidification capacity that can lead to metabolic acidosis;
- recurrent episodes of pyuria.

Hypertension is common during the first few years, even though the plasma creatinine concentration may be normal or only slightly elevated [10-12]. Progressive renal failure ultimately occurs in most patients. However, the glomerular filtration rate follows a fluctuating course. It is often decreased for the first weeks of life, then increases during the first 2 years, remains stable for several years, and then gradually declines. End-stage renal disease usually occurs after 15 years of age [13], although onset between ages 5 and 10 may be seen in children who with manifestations during the first year of life [10].

Liver involvement is always present and may be the predominant clinical feature; in some of these cases, renal ultrasonography may be required to detect clinically silent renal disease. Complications of the hepatic disease include portal hypertension induced by hepatic fibrosis [14] and acute bacterial cholangitis associated with dilatation of the bile ducts [12]. Results of liver function tests usually remain within the normal range. Ultrasonography of the liver reveals dilatation of the peripheral intrahepatic ducts and the main bile ducts. Hepatic cysts may be present and there may also be signs of portal hypertension. Magnetic resonance cholangiography, a noninvasive imaging technique, can also visualize nonobstructive dilations of the intrahepatic bile ducts [15].

Management and treatment

Management of children with ARPKD is supportive. At birth, respiratory distress may require artificial ventilation. Afterwards, blood pressure should be well controlled, eventually with angiotensin-converting enzyme inhibitors. Progressive renal insufficiency should be treated appropriately and renal replacement therapy (dialysis/transplantation) applied at the terminal stage. Cholangitis requires antibiotic therapy and portal hypertension may require therapy.

Etiology

The gene responsible for the disease, *PKHD1*, located on the short arm of chromosome 6 (6p21) [16], has recently been identified. It contains more than 80 exons and codes for a protein called fibrocystin or polyductin but the cellular functions of the gene product (*PKHD1*) remain uncharacterised. [30-33]. There is no evidence of genetic heterogeneity, suggesting

that the marked variability in clinical severity represents differences in phenotypic expression. The kidneys are increased in size with microcysts, usually less than 3 mm in diameter, visible under the capsule. Histological examination of biopsies reveals cystic dilatations, primarily limited to the collecting tubules, with flattening of the epithelium [17,18]. The severity of the renal disease is proportional to the percentage of nephrons affected by cysts. Thus, the ectasia of the collecting tubules is less prominent and irregularly distributed in less severe disease. Larger renal cysts (up to 1 cm) and interstitial fibrosis may be seen in older patients.

Liver involvement in ARPKD is also called congenital hepatic fibrosis [9,19]. The portal spaces are enlarged due to periportal fibrosis and proliferation of the bile ducts, which are dilated and dysgenetic. Hepatocytes are normal. Epithelial growth factors appear to play a significant role in the pathogenesis of cyst growth and formation in ARPKD. In a murine model of this disorder, the administration of an inhibitor of epidermal growth factor receptor tyrosine kinase activity markedly reduced the number of cystic lesions, improved renal function and prolonged survival [20]. When this agent was withdrawn, the rate of progression of cystic lesions was similar to that of untreated animals. The relationship between these observations and the suspect gene is unclear.

Diagnostic methods

Until direct testing for the gene responsible for ARPKD is available, the diagnosis of this disorder is established by ultrasonography, which shows enlarged kidneys that are often more than two standard deviations larger than normal. The kidneys are diffusely hyperechogenic and multiple small cysts may be visible [21]. The cysts may be better visualized on computed tomography (CT), which is more sensitive. Intravenous urography, although less specific, shows large kidneys with radial streaks of contrast medium persisting more than 24 hours after injection. Larger cysts may develop later in life [10,11,22]. Radiological methods may not be sensitive enough to differentiate ARPKD from ADPKD. However, renal pathology provides the diagnosis of ARPKD with cystic dilatation of the collecting ducts with progressive interstitial fibrosis and glomerular sclerosis.

Differential diagnosis

The ultrasonographic appearance may not distinguish autosomal recessive from autosomal dominant disease [23]. In this setting, a careful family history and examination of the parents is

often helpful. Ultrasonography of parents of children with ARPKD will not detect cysts while ADPKD is often first discovered in a parent at the time of diagnosis of the child. However, parents with ADPKD under the age of 25 to 30 may not yet have cysts detectable by ultrasonography and establishing the diagnosis may require evaluation of the grandparents. In addition, extrarenal (hepatic, pancreatic) cysts also favor the presence of autosomal dominant disease, while portal fibrosis or signs of portal hypertension, cholangitis or bile duct dysgenesis favor the diagnosis of autosomal recessive disease.

It should also be recognised that the ultrasonographic finding of enlarged, echogenic kidneys in the fetus is not diagnostic of polycystic kidney disease. Other disorders that can produce these changes include malformation syndromes such as Meckel syndrome, renal dysplasia, congenital nephrotic syndrome and transient nephromegaly in which the ultrasonographic abnormalities return to normal after birth [24].

Genetic counseling

Parents of a child with ARPKD should be informed that each child or new fetus would have a one in four (25%) chance of developing the disease (although the expression of the disease may be different from that in other siblings) and a one in two chance (50%) of being a carrier. Mapping of the *ADPKD* gene and the absence of genetic heterogeneity allow haplotype-based prenatal diagnosis in "at-risk" families. Since this is an indirect diagnosis, its accuracy depends upon the correct diagnosis in previously affected siblings [25]. Older asymptomatic siblings of affected children should be evaluated for hepatic fibrosis.

Antenatal diagnosis

Ultrasonography can also be used for antenatal diagnosis, when performed for some other reason, or for screening [6,26,27]. Most antenatal studies were performed between 31 and 36 weeks of gestation, usually at the request of the parents. Enlarged, hyperechogenic kidneys are the primary finding, but cysts may already be visible [28,29].

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