Clinical characterization of polycystic kidney diseases in infants and children

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Abstract

Polycystic kidney disease (PKD) is an inherited disorder characterized by bilaterally enlarged cystic kidneys without dysplasia. The two major forms, autosomal recessive polycystic kidney disease (ARPKD) and autosomal-dominant polycystic kidney disease (ADPKD), have significant overlap in clinical presentation and radiographic features. This descriptive study was designed to assess the clinical phenotypes of Egyptian infants and children with PKD, presenting to Cairo University Center of Pediatric Nephrology and Transplantation as a referral center. We have studied 36 cases with PKD; 32 patients with ARPKD (89%) and 4 patients with ADPKD (11%). The most important clinical morbidities were urinary tract infection (44%), systemic hypertension (42%), portal hypertension (17%) and end-stage renal disease (ESRD) (14%). Abdominal ultrasonography was the most helpful diagnostic test, while CT scan, renal biopsy and investigations for extra-renal manifestations were required in selected cases. Early and proper diagnosis is important for genetic counseling and for proper management of co-morbidities for better survival and for delaying progression to ESRD.

Key words:

Autosomal recessive polycystic kidney disease, autosomal dominant polycystic kidney disease, inherited renal diseases, chronic renal failure, ultrasonography.
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List of Abbreviations

ACE: Angiotensin converting enzyme
ACEi: Angiotensin-converting enzyme inhibitors
ADPKD: Autosomal dominant polycystic kidney disease
ARPKD: Autosomal recessive polycystic kidney disease
cAMP: Cyclic adenosine monophosphate
CCB: Calcium channel blockers
CHF: Congenital hepatic fibrosis
CKD: Chronic kidney disease
ESRD: End-stage renal disease.
GCKD: Glomerulocystic kidney disease
GFR: Glomerular filtration rate
Hx&E: Hematoxylin and Eosin
ICAs: Intracerebral/intracranial aneurysms
IHBR: Intrahepatic biliary radicles
LVH: Left ventricular hypertrophy
LVMI: Left ventricular mass index
MCD: Medullary cystic disease
MCDK: Multicystic dysplastic kidney
PC-2: Polycystin-2
PKD: Polycystic kidney disease
PKHD1: Polycystic kidney and hepatic disease 1
SPSS: Statistical Package for Social Sciences
TRPP2: Transient receptor potential channel P2
UTI: Urinary tract infection
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Introduction

Polycystic kidney disease (PKD) is an inherited disease that involves bilateral renal cysts without dysplasia. The condition is broadly divided into 2 forms: autosomal recessive polycystic kidney disease and autosomal dominant polycystic kidney disease (Verghese et al., 2012).

Autosomal recessive polycystic kidney disease (ARPKD) is a frequently severe form of pediatric cystic kidney disease that affects the kidneys and the biliary tract. It has an estimated incidence of approximately 1:20,000 live births (Zerres et al., 1998). All typical forms of ARPKD result from mutations in the same gene, PKHD1 (Polycystic Kidney and Hepatic Disease1) (Ward et al., 2002).

The diagnosis of ARPKD can be performed in the intrauterine period, neonatal period or in the first months of life, through ultrasound detection of bilateral diffuse kidney enlargement. Its clinical presentation, however, is highly variable and can be identified in the perinatal, infantile, or juvenile period (Dias et al., 2010).

Pulmonary insufficiency with respiratory distress due to oligohydramnios that is worsened by large renal masses is a major cause of morbidity and mortality in neonates. Babies who survive the neonatal period may still develop chronic kidney disease, which occurs at varying ages depending on the degree of renal involvement but renal prognosis has improved over time because of renal transplantation. Congenital hepatic fibrosis (CHF) still causes considerable morbidity (Verghese et al., 2012).
Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited renal disease, occurring in 1/1000 to 1/500 living births. Two genes have been identified to date: PKD1 which is responsible for the majority of cases and PKD2 responsible for about 15% of cases. The possible existence of a third gene remains under discussion (Peters et al., 1993).

ADPKD is characterized by a progressive cystic enlargement of the kidneys, leading to end-stage renal disease in the fifth or sixth decade, associated to various extra-renal manifestations. It was first denominated “adult polycystic disease” as in the vast majority of cases, no clinical manifestations occur before adulthood. However, the development of renal ultrasonography and other renal imaging techniques enabled this disease to be detected at a presymptomatic stage, and it is currently being diagnosed in children, newborns and even fetuses (Boyer et al., 2007).

**Aim of the work**

The aim of this work was to study the clinical phenotypic features of PKD in infants and children with respect to clinical presentation, chronic kidney disease stage as well as extra-renal associations.
Review

Polycystic kidney disease (PKD) is a ciliopathy that can be diagnosed in adult and pediatric patients. It is an inherited disease that involves bilateral renal cysts without dysplasia. The condition is broadly divided into 2 forms: autosomal recessive polycystic kidney disease (ARPKD), previously known as infantile polycystic kidney disease and autosomal dominant polycystic kidney disease (ADPKD) previously known as adult polycystic kidney disease. ARPKD and 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. The clinical and radiologic manifestations of both types of polycystic kidney disease have considerable overlap (Verghese et al., 2012).

ARPKD is the most common childhood ciliopathy (Avni & Hall, 2010). It is characterized by cystic dilatation of renal collecting ducts associated with hepatic abnormalities of varying degrees, including biliary dysgenesis and periportal fibrosis. The clinical spectrum is variable and depends on the age at presentation, ranging from stillbirth and neonatal demise to survival into adulthood. The most severely affected fetuses have enlarged echogenic kidneys and oligohydramnios attributable to poor fetal renal output. These fetuses develop the "Potter" phenotype, characteristic facies (consists of wide-set eyes, squashed nose, micrognathia, and large, floppy, low-set ears deficient in cartilage) with pulmonary hypoplasia, and deformities of the spine and limbs (Verghese et al, 2012).

Clinical and radiological features suggesting ARPKD rather than ADPKD include neonatal presentation, progression to end-stage renal disease as a child, hepatosplenomegaly, portal hypertension and esophageal varices, bacterial cholangitis, parental consanguinity suggestive of autosomal recessive inheritance,
negative family history and decreased corticomedullary differentiation. (Dell et al., 2009).

**ADPKD** is the most common inherited kidney disease in humans. It is a multisystem disorder characterized by progressive cystic dilatation of both kidneys, with variable extrarenal manifestations in the gastrointestinal tract, cardiovascular system, reproductive organs, and brain (Verghese et al., 2012). Although most ADPKD presents in adulthood, 1%-2% present as newborns, often with signs and symptoms indistinguishable from those of ARPKD (Sweeney & Avner, 2011).

Clinical features suggesting ADPKD rather than ARPKD include positive family history, extrarenal cysts, cerebral aneurysms, asymptomatic presentation, unilateral renal presentation and hematuria (Dell et al., 2009).

Renal ultrasonography may distinguish between the two: bilateral macrocysts are typical of ADPKD. Early in the course of ADPKD, especially in younger children, renal involvement may be unilateral. As ADPKD progresses involvement becomes bilateral; cysts can become massive. Congenital hepatic fibrosis, an invariable finding in ARPKD, is rarely observed in ADPKD (O'Brien et al., 2011).

MRI imaging of the kidneys and liver, may clearly distinguish ARPKD and ADPKD in some cases. Findings on MRI include enlarged kidneys with hyperintense T2-weighted signals. A characteristic hyperintense, linear radial pattern in the cortex and medulla representing microcystic dilatation has been described on RARE-MR urography (Kern et al., 2000).
Although molecular diagnostic testing is available the diagnosis usually relies on imaging studies, a complete family history, clinical findings and, rarely, biopsy findings. Molecular testing for PKD either by linkage analysis or direct sequencing is not recommended for patients in whom a diagnosis can be obtained by imaging analysis alone. Molecular genetic testing for ARPKD and ADPKD is indicated for the subset of patients in whom the clinical and/or tissue diagnosis is equivocal (Sweeney & Avner, 2011).

**Differential Diagnosis**

Differential Diagnosis of Polycystic and/or Echogenic Kidneys in the Pediatric Patient

- Autosomal-recessive polycystic kidney disease (ARPKD)
- Autosomal-dominant polycystic kidney disease (ADPKD)
- Glomerulocystic kidney disease (GCKD)
- **Inherited Disorders Associated with Polycystic Kidneys**: Tuberous sclerosis complex, Meckel_Gruber syndrome, Jeune syndrome and other chondrodysplasia syndromes, Ivemark syndrome, Bardet_Biedl syndrome, oro-facial-digital syndrome Type I, Zellweger cerebrohepatorenal syndrome, Beckwith_Wiedemann syndrome, trisomy 9 and 13, juvenile nephronophthisis/ (MCD) complex, Von Hippel-Lindau Syndrome and Hajdu-Cheney Syndrome
- **Sporadic Disorders Associated with Cystic Kidneys**: Isolated cystic dysplasia, multicystic dysplastic kidney (MCDK), unilateral/localized cystic kidney disease and caliceal diverticula.
- **Miscellaneous Causes of Cystic and/or Enlarged Echogenic Kidneys**: Nephroblastomatosis, bilateral Wilms’ tumor, leukemia or lymphoma, pyelonephritis, glomerulonephritis, radiocontrast nephropathy, bilateral renal
vein thrombosis, transient nephromegaly, congenital nephrotic syndrome, glycogen storage disease and acquired cystic kidney disease (Sweeney & Avner, 2011).

- **Glomerulocystic kidney disease**, a rare disorder that typically presents in the neonatal period with large palpable flank masses, may be clinically indistinguishable from ARPKD. Findings on renal ultrasound examination may also resemble those seen in ARPKD: diffusely enlarged echogenic kidneys and occasional macrocysts. Histologic examination shows dilatation of Bowman's capsule and dysplasia with abnormal medullary differentiation. GCKD also occurs as part of genetic disorders including the tuberous sclerosis complex, orofacial digital syndrome type 1, trisomy 13, brachymesomelia-renal syndrome, and short-rib-polydactyly syndrome (Dell & Avner, 2011).

**Diffuse cystic dysplasia** is characterized by ultrasonographic findings of large echogenic kidneys and histologic findings of disorganized, poorly differentiated nephron segments with primitive elements such as cartilage (Watkins et al., 1999). Diffuse cystic dysplasia can occur sporadically or more commonly as a component of numerous syndromes (e.g., Joubert syndrome, Meckel-Gruber syndrome, Jeune asphyxiating thoracic dystrophy) (Limwongse et al., 1999). In these syndromes, the extrarenal or extrahepatic abnormalities clinically predominate; the diffuse cystic dysplasia remains a more minor feature (Dell & Avner, 2011).

A syndrome of neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, PKD, and congenital glaucoma has been described in two siblings. Liver biopsy confirmed the classic findings of congenital hepatic fibrosis; histologic evaluation of the kidneys was not performed (Dell & Avner, 2011).
Other hepatorenal disorders characterized by renal cystic changes and hepatic fibrosis to consider include a number of disorders already mentioned: juvenile nephronophthisis and multisystem disorders such as Meckel-Gruber syndrome, Bardet-Biedl syndrome, Joubert syndrome, and Jeune asphyxiating thoracic dystrophy Johnson et al 2003. In these autosomal recessive disorders the kidneys are usually small or normal in size, in contrast to the enlarged kidneys of ARPKD (Dell & Avner, 2011).

Medullary cystic kidney disease is characterized by bilaterally shrunken kidneys, cysts restricted to the renal medulla, salt wasting, and polyuria. It is inherited as autosomal dominant trait and is clinically milder, and typically first appear in adulthood (Dell & Avner, 2011).
Autosomal recessive polycystic kidney disease

ARPKD is an inherited disorder characterized by cystic dilations of renal collecting ducts and varying degrees of hepatic abnormalities consisting of biliary dysgenesis and periportal fibrosis (Verghese et al., 2012).

Epidemiology

Based on published reports, the incidence of ARPKD is 1:10,000–1:40,000. The frequency of the gene in the population is estimated to be approximately 1:70. Consistent with autosomal recessive disease, heterozygotes (carriers) are unaffected. The recurrence risk for subsequent pregnancies is 25%, and unaffected siblings have a 66% risk of being a carrier for ARPKD. Males and females are affected equally and ARPKD affects all racial and ethnic groups (Dell et al, 2009).

Molecular genetics

ARPKD is caused by mutations in PKHD1 (polycystic kidney and hepatic disease 1), a large, novel gene that localizes to chromosome 6p21. Intrafamilial variability in ARPKD disease phenotype was originally reported to be unusual in contrast to the wide variability often seen in some ADPKD kindreds. However recent data suggest that up to 20% of ARPKD multiplex pedigrees exhibit significant intrafamilial phenotypic variability. Among families with at least one neonatal survivor, the risk for perinatal demise of a subsequent affected child is 37%. These data are important for appropriate genetic counseling (Dell et al., 2009).

PKHD1
The *PKHD1* gene is an extremely large gene, extending over about 472kb, with the longest open reading frame comprising 67 exons and encoding a protein of 4074 amino acids (*Ward et al.*, 2002).

**Spectrum of Mutations**

More than 270 mutations have been described in the *PKHD1* gene, the majority of which are private. Detection rates of up to 85% have been described in the more severely affected groups, with lower rates in the more moderate cases, which may indicate inclusion of clinical phenotypes not representing ARPKD. Mutations are spread throughout the gene with no evidence of clustering at specific sites (*Furu et al.*, 2004), and include missense, nonsense, frameshift insertion or deletion and in frame deletions as well as mutations altering splicing. Thus, the size and complexity of the *PKHD1* gene in combination with marked allelic heterogeneity and compound heterozygosity makes gene-based molecular diagnostics complicated and not routinely available (*Harris and Rossetti*, 2004).

**Modifier genes**

Recent molecular advances have not answered questions around the factors that modulate gene expression. The variability in clinical phenotype, found even within families, is likely to be influenced by modifier genes as well as the environment. Although a human homologue has not yet been identified, a modifying gene complex on mouse chromosome 4 is suggested (*Mrug et al.*, 2005).

**Genotype-phenotype correlations**

In ARPKD, the combination of mutations is critical to the phenotypic outcome. Patients with two truncating mutations have a lethal phenotype, whereas the presence of at least one missense change can be compatible with life, indicating that many missense changes are hypomorphic alleles that generate partially functional protein (*Rossetti and Harris*, 2007).
**Pathogenesis**

PKHD1 gene encodes several alternatively spliced isoforms predicted to form both membrane-bound and secreted proteins. The largest protein product, termed fibrocystin or polyductin, contains one membrane spanning domain and an intracellular C-terminal tail. Recent reports demonstrate that fibrocystin/polyductin localizes, at least in part, to the primary cilium and the centrosome in renal epithelial cells. The basic defects observed in ARPKD suggest that fibrocystin/polyductin mediates the terminal differentiation of the renal collecting duct and intrahepatic biliary ducts. However, the exact function of the numerous isoforms has not been defined, and the widely varying clinical spectrum of ARPKD may depend, in part, on the nature and number of splice variants that are disrupted by specific PKHD1 mutations (*Guay-Woodford, 2006*).

**Pathology**

In infants and young children, the kidneys are reniform but grossly enlarged. Pinpoint dots are visible on the capsular surface and correspond to cystic cortical collecting ducts. Microscopically the cysts are usually less than 2 mm in size and have been shown to be dilated collecting ducts lined by low columnar or cuboidal epithelium. The glomeruli and other tubular structures appear to be decreased in number because of marked collecting duct ectasia and interstitial edema. Unlike ADPKD, the cystic tubules in ARPKD are fusiform in shape and remain in contact with the urinary stream. In older children the development of larger renal cysts, interstitial fibrosis, and hyperplasia produces a pattern more like ADPKD. Some degree of biliary dysgenesis and hepatic fibrosis is always present in ARPKD. Hepatic involvement is invariably present microscopically at birth. The classic liver lesion shows a typical ductal plate abnormality consisting of portal
fibrosis surrounding increased numbers of hyperplastic, ectatic biliary ducts with normal hepatocellular histology (Dell et al., 2009).

Figure (1) shows cut section in a kidney of a case of ARPKD, the diffuse cystic appearance of the kidneys is noticed.

Figure (2) ARPKD cysts at low power, the radially arranged cysts in collecting tubules of the kidney are seen prominently.