

Chapter 1

Differential Diagnosis of Autosomal Dominant Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disorder characterized by cyst formation and enlargement in the kidney and other organs. There are two known mutations in ADPKD: PKD1 (85% of cases), whose clinical manifestations are the earliest and most rapidly evolving; and PKD2 (15% of cases). PKD1 is a large and complex gene encoding polycystin-1, whereas PKD2 is smaller and encodes polycystin-2. There are a few patients reported in the literature who will not

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fit into any of these subgroups, leading clinicians to question the exact diagnosis, for example, patients without either of these mutations or patients with predominant development of hepatic cysts. The differential diagnosis between ADPKD and other cystic kidney diseases depends on the age of the patient, family history and the presence of associated manifestations. In adult patients in the absence of a family history of ADPKD, doctors should exclude: multiple benign simple cysts; localised or acquired renal cystic disease; medullary sponge kidney; bilateral parapelvic cysts; autosomal recessive polycystic kidney disease (ARPKD); tuberous sclerosis complex (TSC); von Hippel-Lindau disease; autosomal dominant medullary cystic disease; autosomal dominant polycystic liver disease; and X-linked dominant orofaciodigital syndrome type I. In young children, in the absence of family history of ADPKD, it is important to distinguish from ARPKD, contiguous PKD1-TSC2 syndrome or Meckel-Gruber syndrome. This chapter will review the challenges in the diagnosis of multiple kidney cysts in adults, pointing out the most important signs which doctors should be aware of to reach an appropriate diagnosis in this condition.

Key words: Differential diagnosis; PKD1; PKD2; Renal cysts

Introduction

The detection of a single or multiple kidney cysts is very common, especially with advancing age, and it has no particular significance. On the other hand, there are patients who have multiple cysts which, depending on a set of characteristics including age, the number of cysts, and their distribution across several organs, may be included in the so-called polycystic kidney diseases. These diseases are usually genetically-determined and mainly affect the kidneys or the liver (Figure 1). Their differential diagnosis, which is almost always based on imaging criteria, is crucial because polycystic kidney diseases include several clinical entities that have completely different symptoms, evolution and prognosis (1). Early diagnosis allows close supervision and management of kidney function and treatment of associated complications such as hypertension or nephrolithiasis that can delay the progression toward kidney failure (2).

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of monogenic, inherited kidney disease worldwide and affects 1 in 500 to 1000 individuals (3, 4). There are two known genes involved in ADPKD: PKD1 (discovered in 1994) which is

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located on the short arm of the chromosome 16 and produces polycystin 1 (PC1), a transmembrane protein with a long N-terminal extracellular tail that can function as a mechanosensor; and PKD2 (discovered in 1996) which is located on the long arm of chromosome 4 and produces a smaller glycoprotein, polycystin 2 (PC2), that plays a role in calcium transport (3, 5, 6). A small group of all ADPKD families is not linked to either of the known genes, which suggests that there may be a third unknown gene (4). A few reports describe patients with ADPKD phenotype with no mutations in the two described genes (7-12), but some families which previously fit this group when re-evaluated showed a linkage to PKD1 or PKD2 mutations (13-15). Thus, the existence of a third gene for ADPKD is questionable at the present time (4, 6).

The PKD1 mutation accounts for 85% of ADPKD cases in clinically-identified populations, while PKD2 is responsible for the remaining 15% (3, 5, 6). Phenotypes associated with ADPKD show high levels of variability either in terms of age of onset of end-stage kidney disease (ESKD), associated liver disease or other extrarenal manifestations. This can be attributed to genic and allelic heterogeneity and environmental influences (3, 14). Regarding genetic heterogeneity, it is known that PKD1 mutations are associated with more severe disease, including earlier age at diagnosis, increased prevalence of hypertension and earlier onset of ESKD than mutations in PKD2 (median age: 54 vs 74 years old) (3, 4). At the allelic point of view, certain mutations are associated with more severe disease phenotype than others; for example, patients with truncating mutations have a more severe disease than patients with non-truncating mutations (4, 6). Most patients with ADPKD are reported to have truncating mutations (16). A study showed that

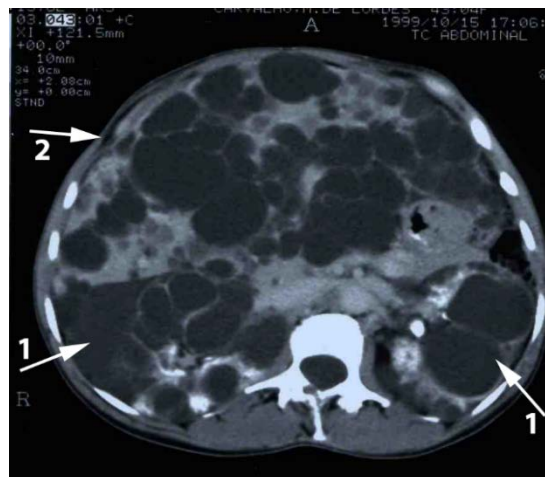


Figure 1. Polycystic kidney and liver disease. 1, Enlarged kidneys due to multiple cysts; 2, Enlarged liver with multiple cysts.

mutations located toward the 5' end of the PKD1 gene are associated with earlier onset of ESKD and increased risk of ruptured intracranial aneurysms (17).

Studies have suggested a gene dose-dependent effect on severity of ADPKD (3, 16). Complete penetrance homozygous mutations in PKD1 or PKD2 in humans are predicted to be embryonically-lethal (16). Although homozygous inheritance of incompletely penetrant PKD1 or PKD2 alleles can be associated with a more severe phenotype, heterozygous inheritance of the same alleles was associated with mild cystic disease (3, 16). The involvement of modifier genes (e.g. endothelial nitric oxide synthesis/ENOS and angiotensin converting enzyme/ACE) and epigenetic regulators (e.g. histone deacetylases/HDACs) may contribute to the complexity of phenotypic variability in ADPKD, since there are studies showing intrafamilial phenotypic variability in families where patients share the same mutation but show significant differences in disease severity and presentation (3).

Diagnosis of ADPKD

Despite constant increase in knowledge of the genetic features of this disease, the screening and diagnosis are based on imaging criteria according to age, family history and number of cysts in individuals (18-21). Ultrasound provides a cheap and safe method for diagnosis and screening of people with a high likelihood of ADPKD, but cost will prevent this screening from being applied to the whole population (6, 16, 22). This led McGovern et al. to identify clinical features that could be used in the early identification of people at high risk of ADPKD (22). The clinical features which best distinguished people with polycystic kidney disease were chronic kidney disease stage 3A or worse, proteinuria, haematuria, diastolic blood pressure (BP) greater than 90 mmHg, and being on multiple antihypertensive medications (22).

In the past the diagnostic criteria were based on patients who had a family history of PKD1. In 2009, the criteria were modified to include patients with a family history of PKD2 who began cyst development at a later age and with a lower number of cysts and at-risk adults of unknown gene type (Table 1) (4, 5, 6, 23). Accordingly, in younger subjects (15-29 years) at-risk because of an affected first-degree relative, three cysts in both kidneys, are sufficient for the diagnosis, whereas in older subjects where the finding of simple cysts is common, 4 or more cysts in both kidneys is required for the definite diagnosis of ADPKD. It is important to note that these unified criteria apply only to patients with positive family history of ADPKD, which excludes about 10-15% of possible ADPKD cases that do not have a family past of ADPKD (5, 6, 16). A positive family history can be absent due to new

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mutations, mosaicism, mild disease from PKD2, non-truncating PKD1 mutations or unavailability of parental medical records (6). In this case, a patient with bilaterally enlarged kidneys and innumerable cysts, without other findings to suggest a different cystic disease (Table 2), most likely has ADPKD (6).

For older subjects, the presence of at least four cysts in each kidney is sufficient for diagnosis of ADPKD regardless of the gene type (4). On the other hand, a few patients who met the diagnostic criteria of ADPKD do not present the expected clinical features, like some degree of renal impairment or the known gene mutations (3, 24, 25). Beyond the most common renal phenotype, Van Gulick et al. described a subset of patients whose hepatic cysts are more prominent than renal cysts and who suffer more from their polycystic liver (> 20 cysts). Occasionally, some of ADPKD patients present with both renal and liver cysts, normal renal function and extensive hepatic disease (24, 25). Cnossen et al. identified the LRP5 gene as the third locus associated with isolated polycystic liver disease. As polycystic liver disease is the most common extrarenal feature in ADPKD patients, it was hypothesised that LRP5 variants may contribute to hepatic and renal disease heterogeneity in ADPKD. Although more studies are needed, it was postulated that LRP5 variants may render ADPKD patients more susceptible to the development of polycystic liver (14). These few cases where diagnosis is not linear means that doctors should be aware of other renal cyst diseases that need to be considered as a differential diagnosis of ADPKD. A substantial number of ADPKD patients progress to ESKD and this condition is responsible for 6-10% of patients in renal replacement therapies. Therefore, early diagnosis is important as treatment of associated complications such as hypertension or nephrolithiasis can delay the progression towards ESKD (2). Moreover, several drugs targeted to specific pathways that are altered in ADPKD were tested recently in randomized-controlled studies and will hopefully be available for human use in the near future (26).

Table 1. Unified criteria for ultrasound diagnosis of ADPKD (4, 5, 6, 23)

Age	Number of cysts	Sensitivity	Positive predictive value
15 – 29 years	A total of 3 cysts in both kidneys	81.7%	100%
30 – 39 years	A total of 3 cysts in both kidneys	95.5%	100%
40 – 59 years	2 or more cysts in each kidney	90%	100%

Table 2. Differential diagnosis of ADPKD (4, 6, 30-34, 36)

Condition	Gene	Inheritance	Prevalence	Differentiating signs/symptoms
Simple renal cysts	--	Acquired	Common	Normal renal function; normal-sized kidneys with smooth contour
Acquired renal cystic disease	--	Acquired	Common	Associated with CKD or ESKD; multiple renal cysts associated with small- to normal-sized kidneys
Medullary cystic kidney disease	MCKD1-2	AD	Unknown	Interstitial fibrosis on renal biopsy. Rarely cysts in the corticomedullary junction; slowly progressive renal failure; small- to normal-sized kidneys; Hyperuricemia, gout
Polycystic liver disease	PRKCSH / SEC63	AD	Unknown	Small number of renal cysts; predominantly liver cystic disease
Autosomal Recessive Polycystic kidney disease	PKHD1	AR	1: 20.000	Early in life kidneys cystic, enlarged and echogenic. With increasing age, kidneys are smaller with macroscopic cysts, nephrocalcinosis and/or small medullary calcifications common; Oligohydramnios (Potter's phenotype) and pulmonary hypoplasia in utero, congenital hepatic fibrosis, Caroli's disease
Tuberous Sclerosis	TSC 1-2	AD	1: 10.000	Angiomyolipoma. Contiguous deletion of PKD1/TSC2 results in severe early onset PKD with ESKD typically occurring in the first 2 decades of life. Skin lesions (facial angiofibromas, periungal fibroma, hypomelanotic macules and Shagreen

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				patch); retinal hamartomas; seizures; mental retardation; cortical tuber; subependymal giant cell astrocytoma; cardiac rhabdomyoma; lymphangiomyomatosis
Von Hippel-Lindau	VHL	AD	1:50.000	High risk of renal cell carcinomas. CNS and retinal hemangioblastomas, pancreatic cysts, pancreatic endocrine tumours, pheochromocytoma
Orofaciodigital syndrome I	OFD1	X-linked, dominant	Very rare (1:250.000)	Embryonic male lethal, cleft palate, bifid tongue, hyperplastic frenula, hypertelorism, broadened nasal ridge, digital abnormalities including syndactyly, CNS malformations
Nephronophthisis	NPHP1-6	AR	1:10.000	Normal-sized kidneys with corticomedullary junction cysts; Interstitial fibrosis; Retinitis pigmentosa; Cerebellar vermis aplasia, polydactyly, occipital encephalocele (NPHP 1 / 6); ocular motor apraxia (NPHP 1-2); liver fibrosis (NPHP2-3), situs inversus (NPHP 2)
Bardet-Biedl syndrome	BBS 1-12	AR	1:140.000	retinal degeneration, childhood obesity, mental retardation, malformations of the urogenital tract, polydactyly
Medullary sponge kidney	Unknown	Unknown	1:5000	Malformation of the distal collecting tubules with nephrolithiasis (haematuria), renal

				function impairment, tubular acidosis, recurrent urinary tract infections
Localised cystic disease	--	Unknown	Unknown (very rare)	Benign disease, unilateral cysts, no progression to chronic renal failure, no extrarenal involvement
Meckel-Gruber syndrome	MGS 1-6	AR	1:13,250 to 1:140,000	Occipital encephalocele, and postaxial polydactyly
Renal cysts and diabetes syndrome	HNF1B	AD	Unknown	Renal malformation, diabetes mellitus, hypomagnesemia, genital tract abnormalities, hyperuricemia and elevated liver enzymes

AD, autosomal dominant; AR, autosomal recessive; CKD, chronic kidney disease; ESKD, end stage kidney disease; CNS, cerebral nervous system.

Direct molecular genetic tests for diagnosis

In most circumstances, diagnosis of ADPKD is based on clinical grounds: history, particularly family history; physical examination; and renal ultrasound. Confirmation of the diagnosis will occur in follow-up studies when an increasing number and size of the renal cysts is evident as well as the appearance of hepatic cysts, hypertension, urologic symptoms and cardiovascular disease. So far genetic studies are not easily available for clinical diagnosis because they are expensive and add no advantage for clinical follow-up (although we expect that this will change with the evidence that there is a correlation between the type of mutation and the prognosis of the disease) (27). Moreover this analysis can be complicated as a result of the duplication of the 1-32 exons of PKD1 gene as pseudogenes in chromosome 16 and the high level of allelic heterogeneity. In general no mutation was identified in about 8% of the families that participated in the HALT-PKD trial (28). Therefore, genetic studies are reserved for a limited number of situations like living-related donors of renal transplant, to exclude the diagnosis of ADPKD in the donor, for pre-natal counselling particularly in the pre-implantation in vitro fertilization and to resolve complex renal cystic disease, if clinically important (27).

Which diagnosis should doctors consider when the patient has multiple renal cysts?

In a majority of cases, establishing a diagnosis of ADPKD is simple. The typical patient presents with enlarged cystic kidneys in the setting of a positive family history (4).

However cystic kidneys in absence of a family history of ADPKD requires a careful review of the history looking for clinical and radiologic aspects that may reveal clinical features of these disorders that are atypical of ADPKD. Table 2 summarises the differential diagnosis of ADPKD.

Renal cysts are common in adults. Finding renal cysts in an ultrasound in an asymptomatic subject raises several options for the diagnosis like simple cysts, ADPKD or acquired renal cysts. Careful history and physical examination, as well as, other clinical findings such as hypertension, liver cysts or renal failure facilitate the differential diagnosis between these common entities. However, in certain circumstances, particularly with atypical clinical presentations the following entities should be excluded:

- *Multiple benign simple cysts:* Prevalence of simple renal cysts increases with age and they are commonly detected with sensitive imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI). MRI-based series detect at least one renal cyst in 93% of subjects 45-59 years of age (4). Spiral CT detected simple renal cysts in 41% of 617 patients. Renal cysts are present in approximately 50% of men (mean age 66 years) and 35% of women (mean age 63 years) (27, 29-30).
- *Localised renal cystic disease:* Localised renal cystic disease is a rare and benign condition. Patients may present hypertension, flank pain, haematuria or flank mass. Clinical features distinguish this disease from ADPKD because of unilateral location, negative family history, no progression to chronic renal failure and no extrarenal involvement (29).
- *Acquired renal cystic disease:* Acquired renal cystic disease is typically detected in individuals with longstanding renal failure and can be found in up to 20% of patients with ESKD (4). The main distinction is the presence of cysts in a normal or small kidney with signs of chronic kidney disease (4, 6).
- *Medullary sponge kidney:* Medullary sponge kidney is a cystic renal disease with unknown inheritance characterised by malformation of the distal collecting tubules with nephrolithiasis, impairment of renal function, tubular acidosis and recurrent urinary tract infections – but rarely evolves to ESKD (32).
- *Bilateral parapelvic cysts:* Parapelvic cysts are a subset of simple cysts that arise within the renal parenchyma adjacent to the renal sinus and account for 5% of all

renal cysts in adults. Clinically they may manifest through obstruction of the ureter or renal pelvis (33).

- *Autosomal recessive polycystic kidney disease:* ARPKD affects 1 in 20000 births and causes neonatal deaths in 30% of patients (6). As the result of a mutation in the PKHD1 gene (31) on chromosome 6, patients usually present in the neonatal period with enlarged, echogenic kidneys with occasional cortical cysts (4, 32). Other perinatal manifestations include Potter's phenotype, pulmonary hypoplasia and portal fibrosis (6, 32). ARPKD is commonly diagnosed at an early age, but adult forms have been described (4). Distinguishing features include bilateral large echogenic kidneys with poor differentiation but, in contrast with ADPKD, with few macrocysts, absence of liver cystic disease but with presence of congenital hepatic fibrosis and/or Caroli's disease (4).
- *Tuberous sclerosis complex:* Tuberous sclerosis complex is an autosomal dominant disease, with incidence 1:5000 to 10 000 and is caused by mutations of the TSC1 or TSC2 gene (4, 32). Family history of the disease is absent in two-thirds of families (6). Mutations of TSC2, which is located tail-to-tail with the PKD1 gene in the short arm of chromosome 16, may result in polycystic renal changes resembling ADPKD, particularly in the so-called contiguous gene syndrome (32). Angiomyolipomas of the kidneys, facial angiofibromas, retinal hamartomas, cerebral pathology (cortical tuber and subependymal giant cell astrocytoma) and benign neurocutaneous tumours allows differentiation (4, 6, 32).
- *Von Hippel-Lindau syndrome:* Autosomal dominant-inherited von Hippel-Lindau (VHL) syndrome is characterised by a combination of hemangioblastomas (retina and cerebellum), renal cell cancers and, less frequently pancreatic, endocrine tumours and pheochromocytoma (4, 32). In the early stage, precancerous renal cysts may occur, which result in enlargement of the kidneys and may be misdiagnosed as ADPKD. However, kidney failure is not a major feature in VHL syndrome (32).
- *Autosomal dominant medullary cystic disease:* Autosomal dominant medullary cystic disease may be present in adulthood (30–60 years) with renal dysfunction and, occasionally, renal cysts (4, 32). The gene involved is uromodulin (encoding Tamm-Horsfall protein) on chromosome 16. Distinguished features are tubular interstitial fibrosis with normal- to small-sized kidneys usually accompanied by early hyperuricemia and gout (4).



Figure 2. Polycystic liver disease. 1, Enlarged liver due to uncountable cysts; 2, Spleen.

- *Autosomal dominant polycystic liver disease:* Autosomal dominant polycystic liver disease is easily mistaken for mild ADPKD, with the main difference being the absence of cystic kidney disease. However, these patients may have few renal cysts leading the clinician to consider a diagnosis of ADPKD, but as a general rule these individuals have predominantly polycystic liver disease and do not develop ESKD (Figure 2) (4). As previously discussed, very few patients with ADPKD present a predominant liver cyst phenotype. When the cysts are also present in the kidneys, the number of liver cysts is small, and a family history of polycystic liver disease or ADPKD is absent, it may be impossible to distinguish the two diseases. Under these circumstances, clinical follow-up and genetic studies may be helpful (34).
- *Orofaciodigital syndrome type I:* This is an X-linked disease due to mutation of the OFD1 gene, and craniofacial and digital defects are associated with polycystic kidney disease (32, 35).
- *Bardet-Biedl syndrome:* Bardet-Biedl syndrome is a very rare disease with incidence 1:140,000, due to diverse mutations in genes coding for proteins involved in the primary cilium functions which entitled this condition as a ciliopathy. Polycystic kidney disease coexists with several extrarenal defects, such as vision loss due to retinal degeneration, childhood obesity, mental retardation, malformation of the urogenital tract and polydactyly (32).
- *Renal cysts and diabetes syndrome:* Type 5 MODY (Maturity Onset Diabetes of the Young) is a rare monogenic disease resulting from mutations in hepatocyte

nuclear factor 1 β (HNF-1 β) that is associated with renal cysts. About 50% of this autosomal-dominant disease results from de novo mutations, and presents with renal cysts or malformation in 90% of patients. It also presents with diabetes mellitus in 45% of patients, genital tract abnormalities and hyperuricemia in 20%, hypomagnesaemia in 40% and elevated liver enzymes in 15% (6).

In children with the finding of renal cysts in absence of a family history of ADPKD, the differential diagnosis should consider the following entities:

- *Autosomal Recessive Polycystic Kidney Disease (ARPKD)*: See detail above.
- *Contiguous PKD1-TSC2 syndrome*: This is a syndrome that results from deletions in the short-arm of chromosome 16 involving both PKD1 and TSC2 genes. These patients usually present in infancy with features of tuberous sclerosis and polycystic kidneys and rapid progression to ESKD. Frequently there is no family history, since the parents are somatic mosaics or results from de novo mutations (4).
- *Meckel-Gruber syndrome*: This is a rare autosomal recessive lethal malformation, characterised by the triad occipital encephalocele, bilateral polycystic kidneys and post axial polydactyly (36).
- *Nephronophthisis*: This condition is characterised by the formation of cysts at the corticomedullary junction without enlargement of the kidneys and generally leads to ESKD before the second decade of life. Numerous extrarenal manifestations are seen, such as Retinitis Pigmentosa, cerebellar ataxia, oculomotor apraxia and hepatomegaly. Six different gene mutations induces this autosomal recessive disease (NPHP1 to NPHP6) a major cause of renal failure in children (32).

Conclusion

ADPKD is a common disease with an important impact on the quality of life and survival of many patients across the world, accounting for 6-10% of patients on renal replacement therapy, making it a burden to families and society. The knowledge about genetic heterogeneity and phenotypic variability is essential for the correct diagnosis and classification. Studies on the genetic development and understanding of the ADPKD pathogenesis have shown an increasing trend, allowing for clarification of the diversity

of clinical and genetic aspects of many patients who do not present classic frames or even the variability within families in patients with the same genetic defect. There are several other disorders that may mimic ADPKD; however, in most cases, additional findings allow an easy differential diagnosis. Atypical ADPKD patients should undergo further evaluation, since management, evolution and prognosis may differ among these disorders.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

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