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Inherited renal cystic diseases

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Abstract

A number of inherited renal diseases present with renal cysts and often lead to end-stage renal disease. With recent advances in genetics, increasing number of genes and mutations have been associated with cystic renal diseases. Although genetic testing can provide a definite diagnosis, it is often reserved for equivocal cases or for ongoing investigational research. Therefore, imaging findings are essential in the routine diagnosis, follow-up, and detection of complications in patients with inherited cystic renal diseases. In this article, the most recent classification, genetic analysis, clinical presentations, and imaging findings of inherited cystic renal diseases will be discussed.

Key words: Hereditary renal disease—Cystic renal disease—Imaging—Polycystic kidney disease

Cystic renal diseases are heterogeneous in origin and pathogenesis, with renal cysts arising from the nephrons and collecting tubules. Abnormal cilium signaling in tubular epithelial cells is thought responsible for cyst formation in many inherited cystic renal diseases. Primary cilia are found on the surface of tubular epithelial cells and function as antennae sensing mechanical, osmotic and chemical stimuli, and signal through many pathways. These pathways control cell proliferation and differentiation, oriented cell division, and planar cell polarity, and are ultimately responsible for maintaining the normal tubular structure [1]. Disruption of these signaling pathways leads to ectatic or cystic nephrons and collecting ducts and cyst development [2].

Inherited cystic renal diseases include autosomal-dominant polycystic kidney disease (ADPKD), due to *PKD1* and *PKD2* mutations, and autosomal recessive polycystic kidney disease (ARPKD), due to *PKHD1* mutations. Related diseases are autosomal-dominant tubulointerstitial kidney disease (ADTKD), which is a new terminology that includes various rare genetic diseases now classified by the gene involved (please refer to III. Autosomal-dominant tubulointerstitial kidney disease) (Table 1). Glomerulocystic kidney disease (GCKD), a genetically and phenotypically heterogeneous entity, often presents with renal cysts. Medullary sponge kidney (MSK), which is normally considered sporadic but may have an inherited component, can be associated with medullary cysts. Autosomal-dominant polycystic liver disease (ADPLD), a distinct genetic disorder with multiple hepatic cysts but no or few renal cysts, caused by mutations to the *PRKCSH*, *SEC63*, or *LRP5* genes, may be confused with ADPKD. Some hereditary tumor syndromes, including tuberous sclerosis complex (TSC) and von Hippel–Lindau disease (VHL), are associated with an increased risk for renal cysts and benign or metastatic tumors. In this article, all of these inherited cystic renal diseases will be described with the responsible genes and proteins, as well as clinical and radiological presentations (summarized in Table 1).

In evaluating inherited cystic renal diseases, the radiologic findings, including the distribution and morphology of the renal cysts and other organ involvement, are essential for the diagnosis. The genetic testing can be valuable when the diagnosis is equivocal or a definite diagnosis is needed, but as with all testing is not informative in every case.

Autosomal-dominant polycystic disease (ADPKD)

Clinical and genetic description

ADPKD is the most common inherited renal disease with an estimated prevalence of 1 in 1000 live births and is inherited as an autosomal-dominant trait. Approximately 90 % of cases have a family history, but in 5–10 % of families, a de novo mutation is suspected. It is commonly associated with end-stage renal disease (ESRD) and accounts for ~5 % of ESRD population in the

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Table 1. Genes and proteins for common inherited cystic renal diseases, and associated extrarenal manifestations

Disease	Freq.	Chromosome	Gene	Protein	Function	Extrarenal manifestation
ADPKD	1:1000 (AD)	16p13.3	*PKD1*	Polycystin 1 (cilium)	Cell membrane/ciliary receptor	Cysts in other organs, intracranial & aortic aneurysm, mitral valvular prolapse
		4q21.2	*PKD2*	Polycystin 2 (cilium, ER)	Ciliary/intracellular Ca^{++} channel	
ARPKD	1:20,000 (AR)	6q21.2	*PKHD1*	Fibrocystin or polyductin (cilium)	Cilia, Membrane receptor	Hepatic fibrosis, Caroli syndrome
NPHP	1:50,000 (AR)	various	*19 described genes*	various	Regulate protein trafficking to cilia	Retinitis pigmentosa, cerebellar aplasia, ocular motor apraxia
ADTKD-UMOD	? (AD)	16p12.3	*UMOD*	Uromodulin	Urinary secreted protein	None
ADTKD-MUC1	? (AD)	1q21	*MUC1*	Mucin-1	Lines surface of epithelial cell	Hyperuricemia, gout
ADTKD-REN	? (AD)	1q32.1	*REN*	Renin	Mediates extracellular volume	Hyperuricemia, gout
ADTKD-HNF1B	? (AD)	17q12	*HNF1b*	Hepatocyte nuclear factor 1-β	Nephron & fetal pancreas development	Pancreatic hypoplasia, genital tract malformation
VHL	1:35,000 (AD)	3p25	*VHL*	pVHL (base of cilium)	Inhibits HIF-1α, planar polarity & ciliogenesis	Retinal hemangioma, cerebellar hemangioblastoma, pancreatic cysts & islet cell tumor, pheochromocytoma, epididymal cystadenoma
TSC	1:6000 (AD)	9q34.3	*TSC1*	Hamartin	Suppress mTor activity	Angiofibroma, ungual fibroma, retinal hamartoma, subependymal giant cell astrocytoma, cardiac rhabdomyoma, pulmonary lymphangioleiomyomatosis
		16p13.3	*TSC2*	Tuberin	Suppress mTor activity	
ADPLD	$<$1:10,000 (AD)	19p13	*PRKCSH*	Hepatocystin	Quality control of newly synthesized glycoproteins	Hepatic cysts without renal cysts
		6q21	*SEC63*	Sec63	Integral ER membrane protein	

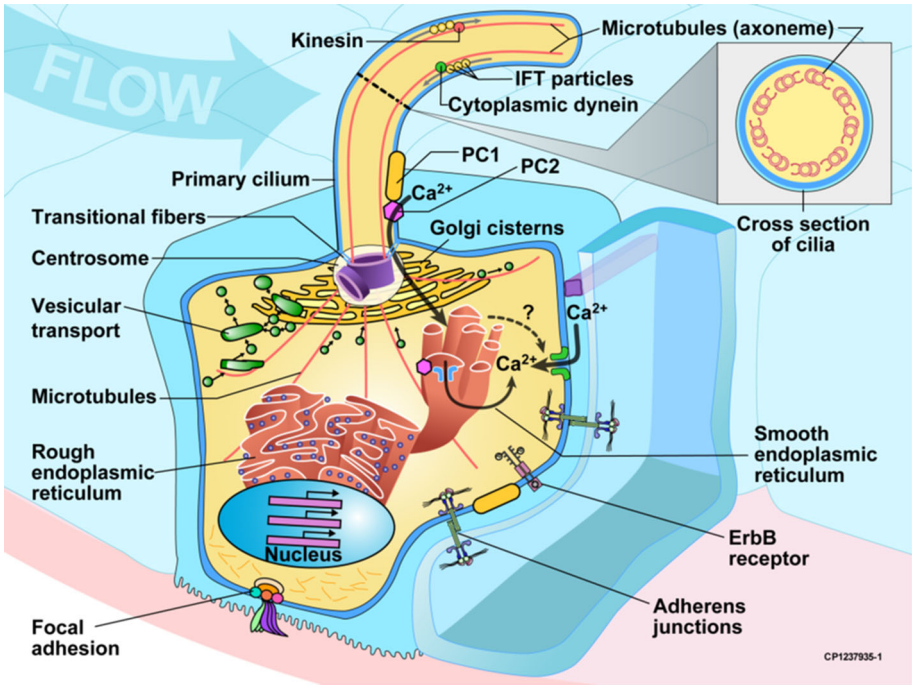

Fig. 1. Diagram demonstrating the primary cilium and locations of the polycystins (PC). PC1 and PC2 are found on the primary cilium, a single hairlike structure that projects into the lumen. In response to mechanical stimulation of the primary cilium by flow, the PC1 and PC2 complex mediates Ca^{++} entry into the cell, which triggers Ca^{++}-induced Ca^{++} release from the smooth ER. PC1 is located predominantly in the cilia and plasma membrane, whereas PC2 is located predominantly in the ER as well as cilia. PC2 is an intracellular Ca^{++} channel. (Reproduced from Ref. [32] with permission).

United States and ~10 % in the European Union. Although ADPKD is most commonly diagnosed in 4th and 5th decades of life, imaging studies can detect the disease in the majority of affected children [3].

Two genes have been identified: *PKD1* gene is responsible in 85 % of cases and located on the short arm of chromosome 16 (16p13.3), and *PKD2* gene comprises up to 15 % of cases and is located on the long arm of chromosome 4 (4q21.2). It is uncertain whether there is further genetic heterogeneity accounting for a small proportion of cases. Polycystin 1 (PC1) and 2 (PC2) are the proteins encoded by *PKD1* and *PKD2*, respectively. PC1 is located predominantly in the primary cilia and plasma membrane, whereas PC2 is located predominantly in the endoplasmic reticulum (ER) as well as the primary cilia (Fig. 1) [4]. PC2 functions as a calcium channel and PC1 may regulate that channel.

Patients with *PKD1* mutations have earlier onset of symptoms and earlier age of ESRD than those with *PKD2* mutations. Patients with *PKD1* and *PKD2* mutations typically present clinically in their 30′s and 50′s, respectively, and reach ESRD in their 50's and 70's, respectively (Fig. 2). PKD2 patients develop fewer cysts but have a similar renal growth rate compared to PKD1 cases [5]. The prevalence and age of diagnosis of hypertension are lower and hematuria is less common in PKD2 [6]. Recently described allelic effects indicate that PKD1 patients with mutations predicted to truncate PC1 have more severe disease than non-truncating cases [7].

Marked intrafamilial and interfamilial phenotypic variability is seen in patients with ADPKD, which is not only partly related to the gene and mutation involved, but also associated with genetic background and environmental modifiers (dietary factors like salt intake and possibly hydration, smoking, etc.).

As the *TSC2* gene locus is adjacent to *PKD1* in 16p13.3, deletions affecting both genes may cause the *TSC2*/*PKD1* contiguous gene syndrome. The affected patients (usually children) have severe cystic renal disease and angiomyolipomas in the kidney (Fig. 3) as well as skin, CNS, and other lesions characteristic of TSC.

Patients may present with hypertension (almost universally by the time of ESRD), flank or back pain (60 %), hematuria, proteinuria, and later ESRD. Decreased urinary concentration and reduced blood flow can be seen in early stage of the disease. Hypertension may be related to vascular functions of PC1 and PC2 as well as ischemic changes related to stretching and deformation of the renal vasculature with associated activation of the renin-angiotensin system [8]. Pain may be associated with hemorrhage, infection, or stone formation. Hemorrhage is very common with renal cysts and typically demon-

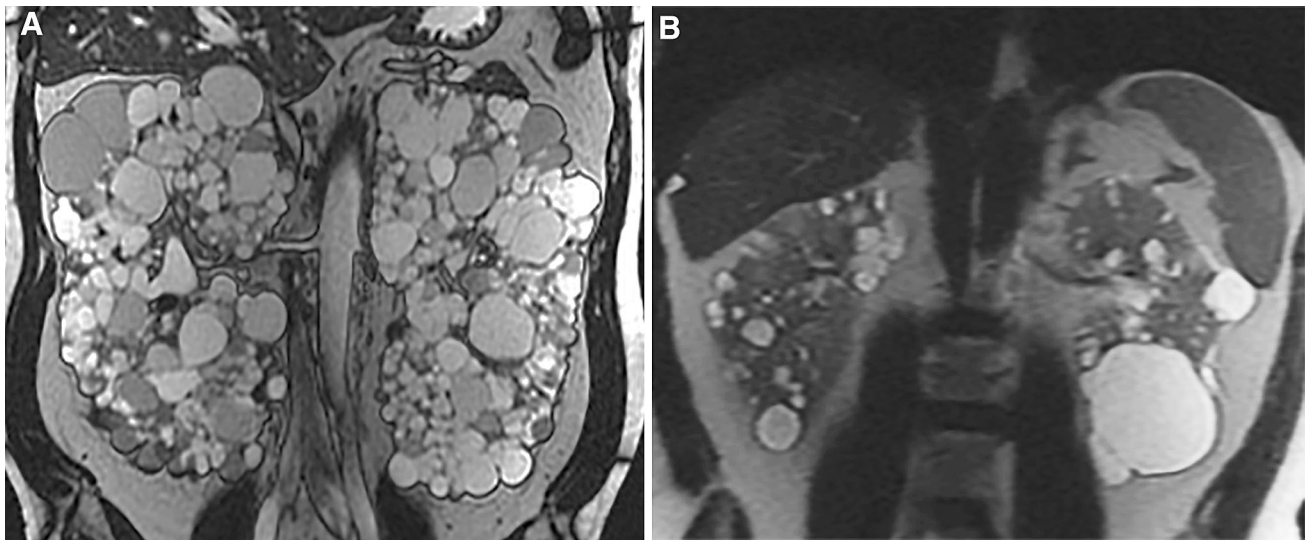

Fig. 2. PKD1 (**A**) and PKD2 (**B**) in two 43-year-old males. The kidneys are markedly enlarged and the renal architecture is distorted by innumerable cysts in (**A**), whereas the renal cysts are fewer and the renal contour and architecture are relatively preserved in (**B**).

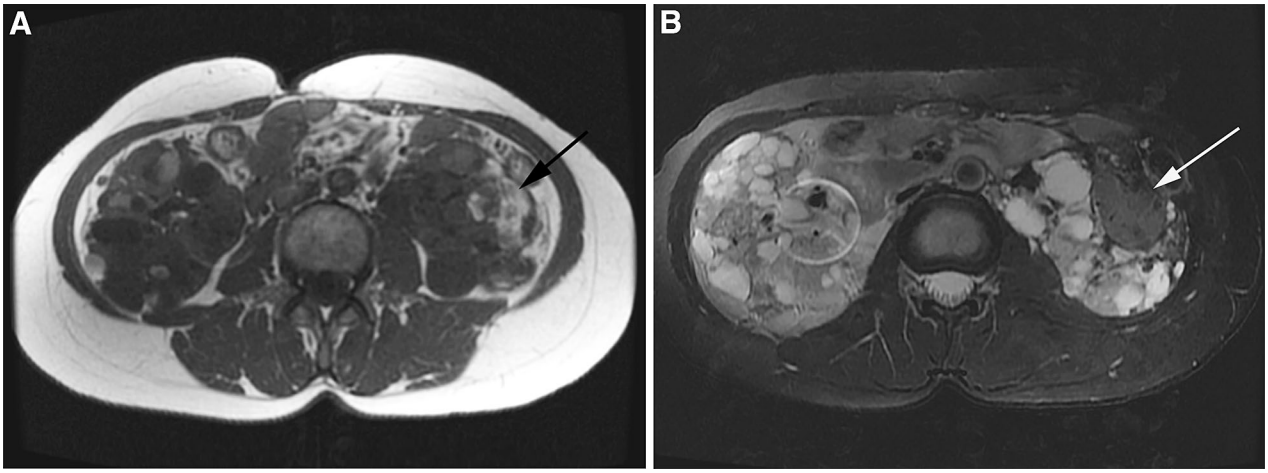

Fig. 3. TSC2/PKD1 contiguous gene syndrome in a 51-year-old female. Axial T1 (**A**) and T2-weighted images (**B**) demonstrate multiple bilateral renal cysts consistent with autosomal-dominant polycystic kidney disease. There is a mass demonstrating T1 hyperintensity and T2 hypointensity in the lower left kidney (*arrows*) consistent with fat-abundant angiomyolipoma. This patient has a large deletion disrupting *TSC2* and *PKD1* with mosaicism.

strates T1 hyperintensity on MRI. Sometimes a hemorrhagic cyst can rupture into the renal sinus or perinephric space (Fig. 4). Hematuria may be related to cyst hemorrhage, infection, cystitis, or stones and is generally associated with a poor renal outcome. Renal stones are seen in ~20 % of cases, with the most common stone composition being uric acid and calcium oxalate [9]. Not infrequently these stones are difficult to differentiate from cyst wall calcifications. Dual energy CT can be helpful in differentiating uric acid from non-uric acid stones (Fig. 5).

Radiological description

In ADPKD, the bilateral kidneys are enlarged with multiple cysts. The renal cysts are typically bilateral and diffuse; however, a small number of patients (2–9 %) show atypical distributions including unilateral, segmental, asymmetric, and lopsided involvement (Fig. 6) [10]. Very rarely, when renovascular disease or urinary tract obstruction is superimposed, marked atrophy of the parenchyma may result in a small polycystic kidney (Table 2) [10]. It has been speculated but not proven that

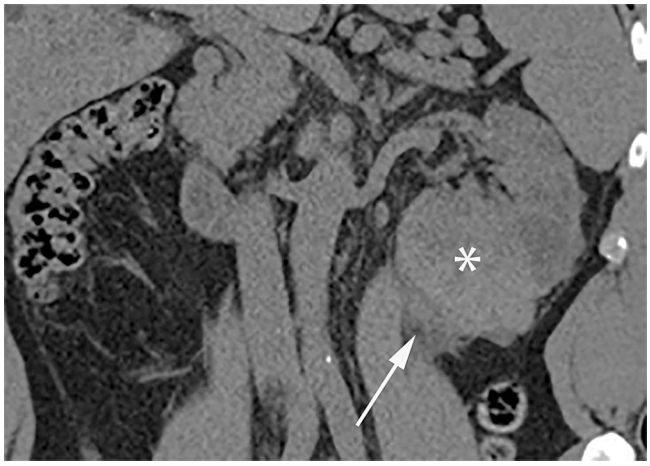

Fig. 4. ADPKD with a ruptured hemorrhagic cyst in a 54-year-old male. Coronal reconstruction of noncontrast CT demonstrates a hemorrhagic cyst (*asterisk*) in the lower left kidney with perinephric fat stranding (*arrow*). Hemorrhage within the renal cysts is very common but infrequently these cysts can rupture into the renal sinus or perinephric space.

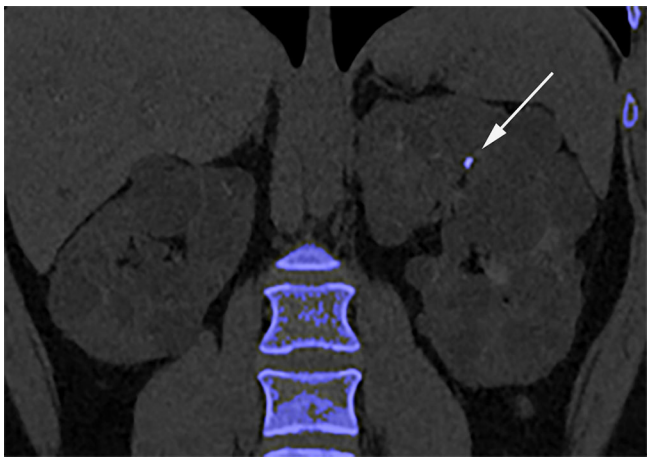

Fig. 5. ADPKD with a calcium stone in a 42-year-old male. Coronal reconstructing image of noncontrast dual energy CT of the kidneys demonstrates a small stone in the upper pole of the left kidney with a *blue color map* indicating non-uric acid composition. Multiple renal cysts are seen in both kidneys. Depiction of urinary stones and characterization of the stone composition can be achieved by dual energy CT. Stone formation is common in patients with ADPKD, with the uric acid and calcium oxalate being most common composition.

unilateral or markedly asymmetric polycystic kidneys are due to genetic mosaicism.

The consortium of imaging studies of polycystic kidney disease (CRISP) followed 241 patients with ADPKD with yearly MRI for three years and found that total and cyst volume increase exponentially in the affected patients [11]. The study also demonstrated that renal and cyst enlargement precedes and predicts the decline of renal function and that the kidney volume is the strongest predictor of renal functional decline (the larger the renal volume, the greater the loss of renal function). In addition, CRISP found that a decrease in renal blood flow preceded and was an independent predictor of the decline in glomerular filtration rate (GFR) [12].

The diagnosis of ADPKD is most often determined by imaging studies including US, CT, and MRI. US is most commonly used as an initial screening method in individuals with a positive family history. As patients with *PKD2* mutation and non-truncating *PKD1* mutations typically show less severe disease, the diagnostic criteria for *PKD1* truncating mutations perform suboptimally for patients with in the other mutation groups. Revised criteria for at-risk individuals of unknown genotype (*PKD1* or *PKD2*) include at least three (unilateral or bilateral) renal cysts for individuals of 15–39-year old, two or more cysts in each kidney for individuals of 40–59-year old, and four or more cysts in each kidney for individuals of 60-year old or older [13]. These criteria have been reported to have 100 % positive predictive values [13]. In contrast, fewer than two cysts in at-risk individuals of 40-year old or older is sufficient to exclude ADPKD with reported negative predictive value of 100 % [13]. CT and MRI are more sensitive in depicting renal cysts and can be helpful in equivocal cases. A recent study has shown that finding of fewer than five renal cysts by magnetic resonance imaging (MRI) is sufficient for disease exclusion [14]. Genetic testing can be performed when imaging findings are equivocal or a definitive diagnosis is needed. Using direct sequencing, mutation detection can be made in 85–95 % cases [5, 15].

Cyst infection is more common in females than males and often caused by Enterobacteriaceae. Contrast-enhanced CT or MRI demonstrates a fluid–fluid level, cyst wall thickening and enhancement, heterogeneous or increased density, or an air bubble. When findings are equivocal, these lesions can be further evaluated with ^{67}Ga or ^{111}In-labeled leukocyte scans or ^{18}F-fluorodeoxyglucose (FDG) PET/CT (Fig. 7) [16]. The radiotracers of the leukocyte scans are excreted through the liver and spleen and may possibly obscure hepatic lesions, whereas FDG is excreted through the kidneys on PET/CT and may obscure renal lesions. For confirmation and treatment, US- or CT-guided cyst aspiration can be performed.

The incidence of renal cell carcinoma (RCC) generally does not appear higher than the general population [17], although some patient series did find a higher incidence in ADPKD [18]. Earlier age at presentation, frequent constitutional symptoms, and higher rates of sarcomatoid, bilateral, multicentric, and metastatic tumors have been reported [17]. In ADPKD patients, the solid appearance, contrast enhancement, heavy calcifications, restricted diffusion on MRI, tumor thrombosis, and lymphadenopathy can be helpful for the diagnosis of

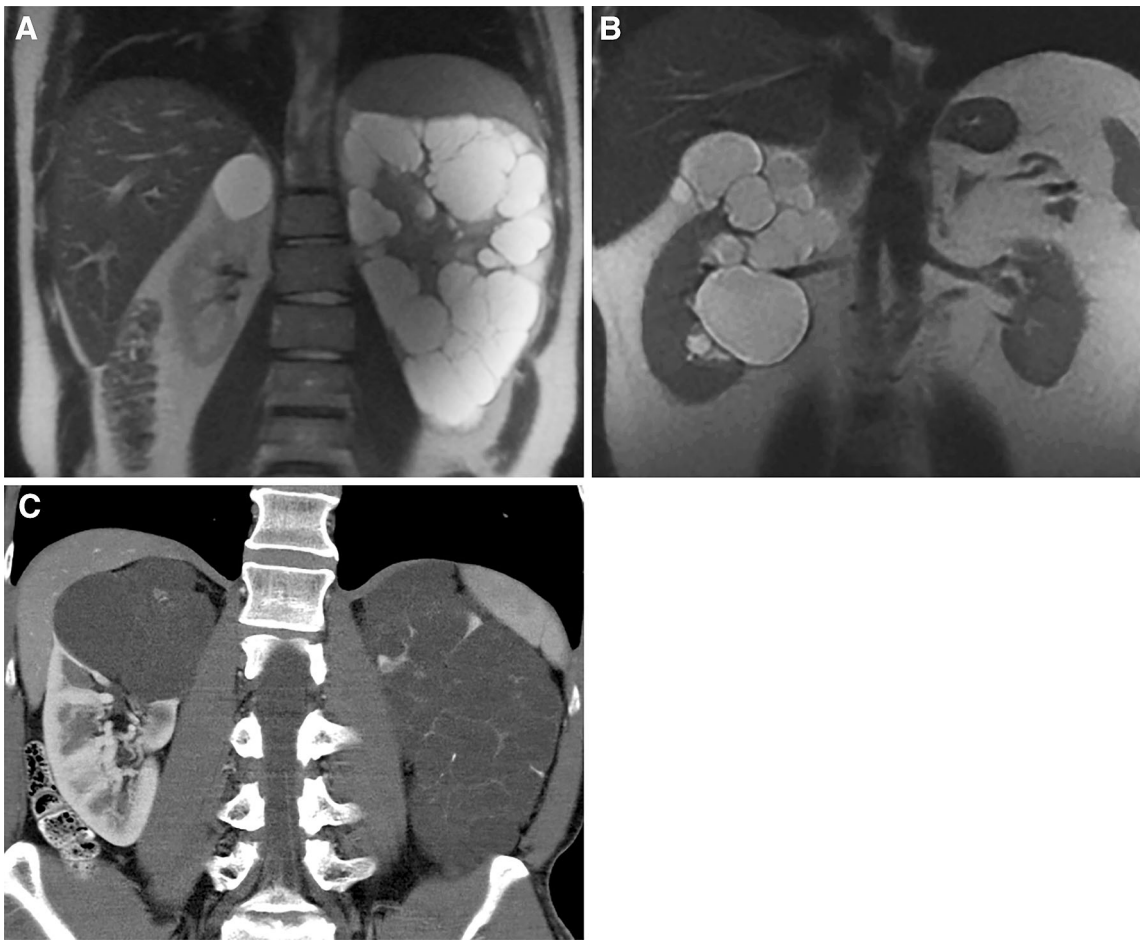

Fig. 6. Atypical presentation of ADPKD in three different patients. **A** Unilateral (22-year-old male). **B** Segmental (52-year-old male), **C** Asymmetric involvement (59-year-old male). (Reproduced from Ref. [14] with permission).

Table 2. Classification of ADPKD patients by imaging findings [10]

Class, subclass, and term description	
1: Typical ADPKD	Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to total kidney volume (TKV)
2: Atypical ADPKD	
A	
Unilateral	Diffuse cystic involvement of one kidney causing marked renal enlargement with a normal contralateral kidney defined by a normal kidney volume (<275 ml in men; <244 ml in women) and having no or only 1–2 cysts (Fig. 6a)
Segmental	Cystic disease involving only one pole of one or both kidneys and sparing the remaining renal tissue (Fig. 6b)
Asymmetric	Diffuse cystic involvement of one kidney causing marked renal enlargement with mild segmental or minimal diffuse involvement of the contralateral kidney defined by a small number of cysts (>2 but <10) and volume accounting for <30 % of TKV (Fig. 6c)
Lopsided	Bilateral distribution of renal cysts with mild replacement of kidney tissue with atypical cysts where ≤5 cysts account for ≥50 % TKV (the largest cyst diameter is used to estimate individual cyst volume)
B	
Bilateral presentation with unilateral atrophy	Diffuse cystic involvement of one kidney causing moderate to severe renal enlargement acquired with contralateral acquired atrophy
Bilateral presentation with bilateral kidney atrophy	Impaired renal function (serum creatinine ≥1.5 mg/dl) without significant enlargement of the kidneys, defined by an average length <14.5 cm, and replacement of kidney tissue by cysts with atrophy of the parenchyma

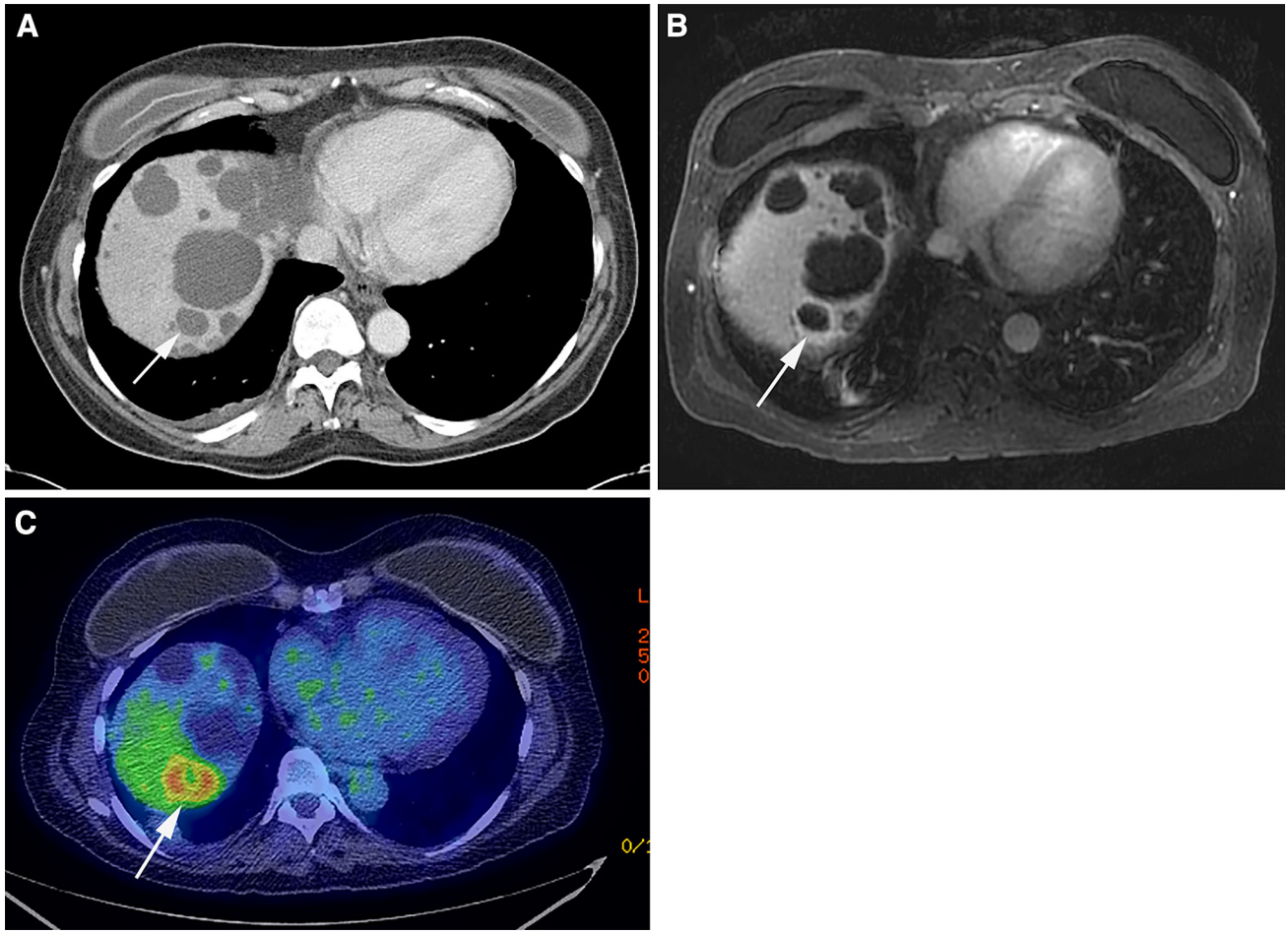

Fig. 7. ADPKD with an infected liver cyst in a 59-year-old female. **A** Axial contrast-enhanced CT demonstrates multiple cysts in the liver. The small cystic lesion in the posterior right liver dome (*arrow*) demonstrates mildly heterogeneous internal attenuation but no discrete rim enhancement. **B** Axial contrast-enhanced T1-weighted MRI sequence demonstrates high-signal intensity rim around the cyst (*arrow*). **C** PET/CT shows rim-shaped FDG avidity along the cyst wall. Cyst infection was confirmed by aspiration. Cyst infection is an uncommon complication of ADPKD. The diagnosis of cyst infection is often difficult on CT or MRI, but can be facilitated using PET/CT.

the rare cases of RCC (Fig. 8). The diagnosis, however, is often difficult due to innumerable renal cysts and associated anatomic distortion.

Cysts in other organs are commonly seen, most frequently in the liver. The hepatic cysts are seen in more than 90 % of cases in later stage. ADPLD can occur as a distinct genetic disorder, which presents with liver cysts without or with few renal cysts, with three genes (PRKCSH, SEC63, or LRP5) implicated. Hepatic cysts are more common and more severe in females, especially with a history of multiple pregnancy or prolonged use of oral contraceptives, likely related to an estrogen effect. Cysts are seen in other organs including the pancreas (5 %), arachnoid membrane (8 %), and seminal vesicles (40 %) (Fig. 9) [2]. Ovarian cysts are not associated with ADPKD.

Vascular complications associated with ADPKD include intracranial aneurysm (ICA), dolichoectasia, thoracic aortic and cervicocephalic artery dissection, and coronary artery aneurysm. Intracranial aneurysm occurs in 4–8 % of asymptomatic ADPKD patients, but the incidence is higher with a family history of nonruptured (10 % risk) or ruptured ICA (20 % risk) [19]. Rupture occurs in half of the patients with an ICA during their lifetime and causes significant mortality and morbidity. In ADPKD patients, ICA commonly involves the anterior circulation as in the general population and is often multiple. ICA rupture occurs at an earlier age than in the general population (39 vs. 51 years) [2]. Screening for ICA is indicated in an asymptomatic ADPKD patient with a family history of ICA, high-risk occupations and when needed for reassurance. Screening is also indicated in patients with a previous history of subarachnoid hemorrhage because they are at higher risk for de novo aneurysms. Screening is commonly done by MR angiography (which does not require contrast enhance-

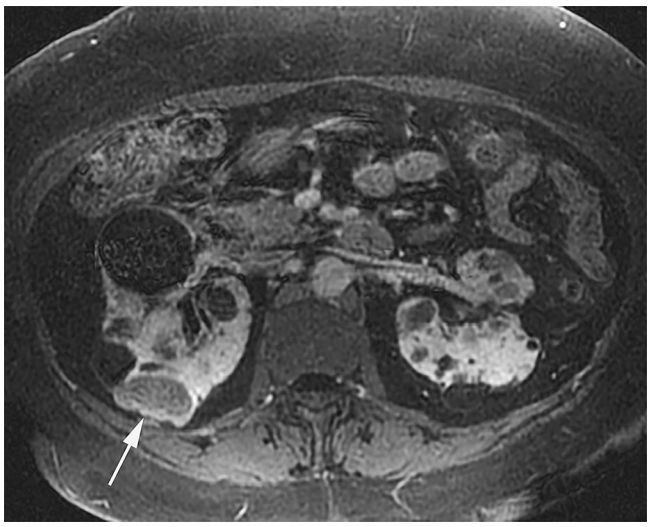

Fig. 8. ADPKD with renal cell carcinoma in a 56-year-old female. Axial contrast-enhanced MR image demonstrates a solid appearing, mildly enhancing lesion in the posterior aspect of the mid right kidney (*arrow*). Pathology confirmed the diagnosis of papillary renal cell carcinoma. The diagnosis of associated RCC in ADPKD patients is often difficult. Contrast enhancement, diffusion restriction, or identification of tumor thrombus or lymphadenopathy can be helpful for the diagnosis.

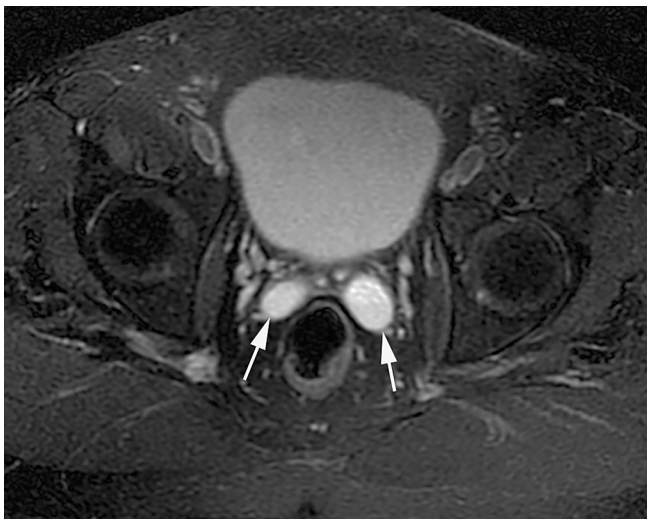

Fig. 9. ADPKD with bilateral seminal vesicle cysts in a 35-year-old male. Axial T2-weighted MR image demonstrates bilateral seminal vesicle cysts (*arrows*).

ment) or CT angiography (which requires contrast enhancement).

Mitral valvular prolapse, aortic root dilatation and valve insufficiency, colonic diverticulosis and diverticulitis, and bronchiectasis are more prevalent in ADPKD patients than in the general population.

CT or MRI can be used for renal volume measurement, depiction of other organ involvement, and diagnosis of complications such as hemorrhage, infection, stone formation, and associated malignancy. Renal volume measurement can be performed by simply multiplying three perpendicular measurements using an ellipsoid formula ($\pi/6 \times A \times B \times C$) (Fig. 10A, B), or using planimetry (Fig. 10C) or stereology (Fig. 10D). Volumetric analysis of the renal cyst and renal volume is an important tool in evaluating cyst growth and predicting the renal functional changes.

Treatment is mainly focused on lowering morbidity and mortality from the complications of the disease, and includes control of hypertension and pain, antimicrobial therapy for infected cyst, stone removal or dissolution, cyst aspiration without or with sclerosis, cyst fenestration, nephrectomy, partial hepatectomy or segmentectomy, dialysis, and renal transplant. A few drugs have been shown to be of value for treatment of polycystic disease in animal models and/or clinical trials, including vasopressin V2 receptor antagonists such as tolvaptan and somatostatin analogs such as octreotide and lanreotide.

Autosomal recessive polycystic kidney disease (ARPKD)

Clinical and genetic description

ARPKD is inherited as an autosomal recessive trait and occurs with an incidence of 1 in 20,000. Siblings of an affected individual have a 25 % chance of being affected, whereas the carrier parents are unaffected. The *PKHD1* gene is located on the short arm of chromosome 6 (6p21.1), and the protein product called fibrocystin or polyductin is a membrane-associated protein located in the primary cilia [19]. In ARPKD nephrogenesis is normal, but the collecting ducts grow excessively. Pathologically diffuse fusiform dilatation of the collecting ducts is characteristic of the classical, early presentation of the disease. In the patients who survive infancy, the kidneys become increasingly fibrotic over time with a relative reduction in volume and development of macroscopic cysts.

ARPKD affects both the kidneys and liver. Although clinical presentation of ARPKD is variable, severely affected patients are often identified in utero or at birth. Poor fetal renal output results in oligohydramnios and may be associated with pulmonary hypoplasia. Thirty percent of affected newborn die within the first week [20]. Less severely affected patients survive to later life. Severe renal damage with mild liver damage is often seen in the fetus and newborn, whereas more severe liver damage with milder renal damage is seen in later life. Hypertension is seen approximately 65–75 % of affected children [20], and chronic renal insufficiency and ESRD occur frequently.

Patients who survive the neonatal period often live to adulthood. Adeva et al. found in their study of 65

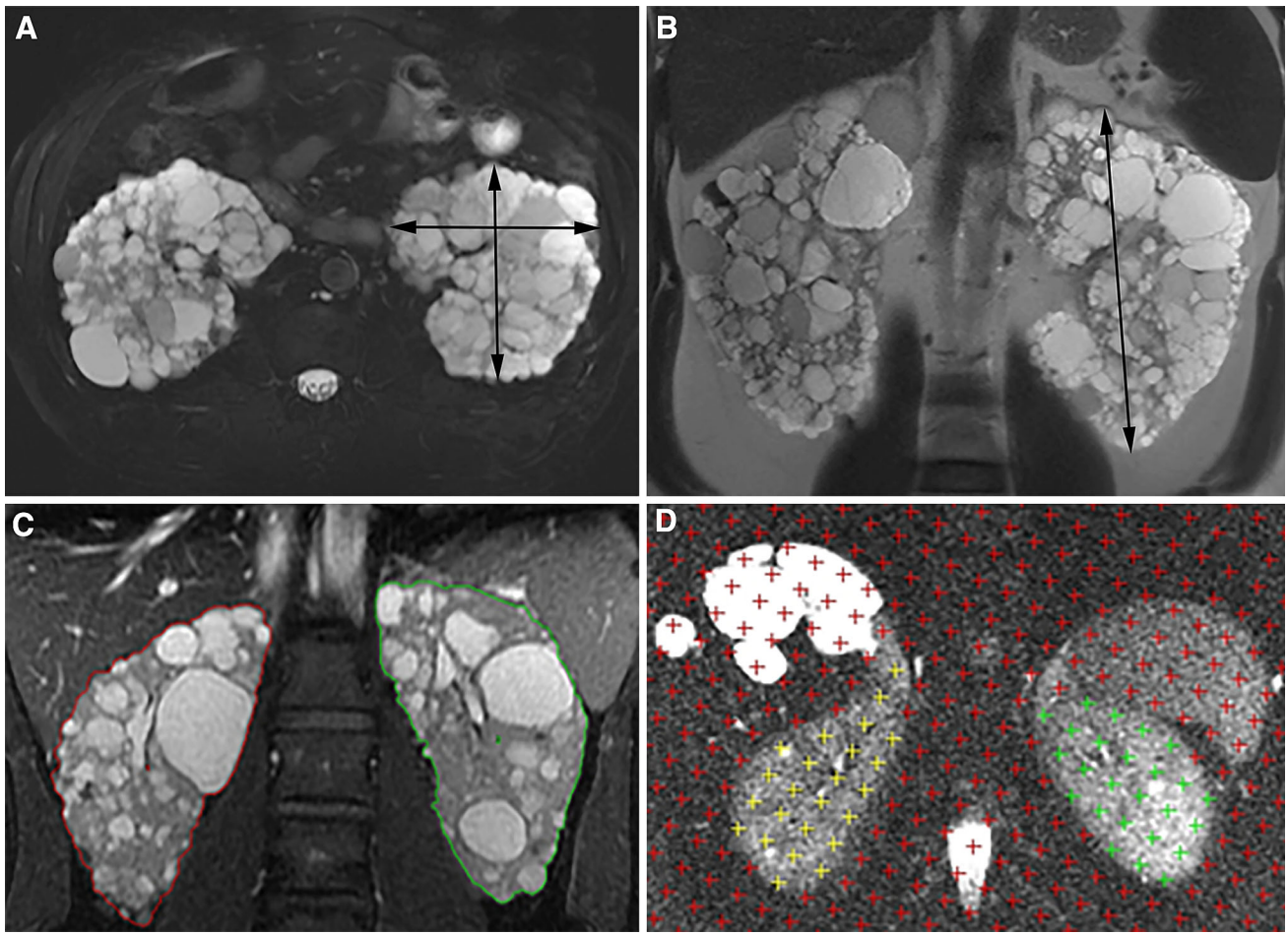

Fig. 10. Renal volume measurement. **A**, **B** Axial and coronal T2-weighted images of the kidneys. The renal volume can be easily measured by multiplying three perpendicular dimensions of the kidney using an ellipsoid formula ($\pi/6 \times A \times B \times C$). **C** Using planimetry, the renal volume can be measured by multiplying manually or automatically drawn plane areas and section thickness. **D** Stereology is the three-dimensional interpretation of two-dimensional cross sections of materials. Using this techniques, renal or hepatic volumes can be calculated. The right kidney is marked with *yellow markers and left kidney with green markers*.

patients with ARPKD that approximately one-third of the patients presented at less than 1 year of life ($n = 22$), one-third at 1–20 years ($n = 23$), and the other one-third greater than 20 years ($n = 20$), and that 20-year survival after the diagnosis was 36, 80, and 88 %, in each group, respectively [21]. Hepatic manifestations include congenital hepatic fibrosis and Caroli syndrome associated with portal hypertension or ascending cholangitis.

Radiological description

The diagnosis is often made by a combination of a negative family history and radiologic findings, commonly using fetal or neonatal US or MRI (Figs. 11, 12). The typical neonatal presentation of the disease on US is bilateral enlargement, diffusely increased echogenicity and loss of corticomedullary differentiation (Fig. 11). This is likely attributed to increased acoustic interfaces produced by innumerable 1–2 mm collecting duct cysts. Although the characteristic imaging findings are suggestive of the diagnosis, the imaging findings are not specific and early-onset ADPKD or other cystic renal diseases should also be considered. Typically the kidneys in ARPKD patients are more echogenic than the liver and contain cysts smaller than 1 cm, whereas the ADPKD kidneys are less echogenic than the liver and renal cysts are larger than 1 cm [22]. Unlike the kidneys in ADPKD, the ARPKD kidneys often show a uniform sponge-like appearance with much smaller cysts related to dilated collecting ducts and retain a reniform shape (Fig. 12). With increasing age, the kidneys become smaller and macroscopic cysts may appear. As interstitial fibrosis progresses, US may demonstrate increased echogenicity and an irregular renal contour [21]. Nephrocalcinosis and/or small medullary stones are common and MSK can be seen [21]. In children or young

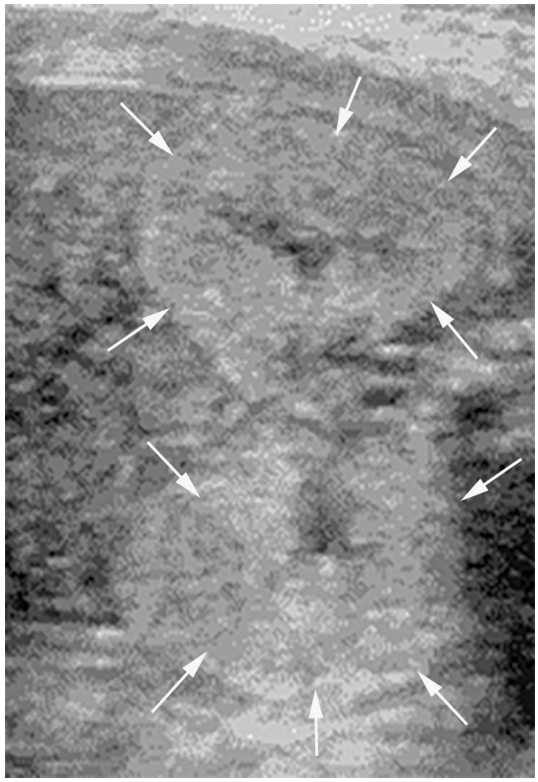

Fig. 11. ARPKD in a fetus. Fetal US demonstrates enlarged bilateral kidneys with increased echogenicity and loss of corticomedullary differentiation (*arrows*), likely caused by increased acoustic interfaces produced by tiny innumerable cysts.

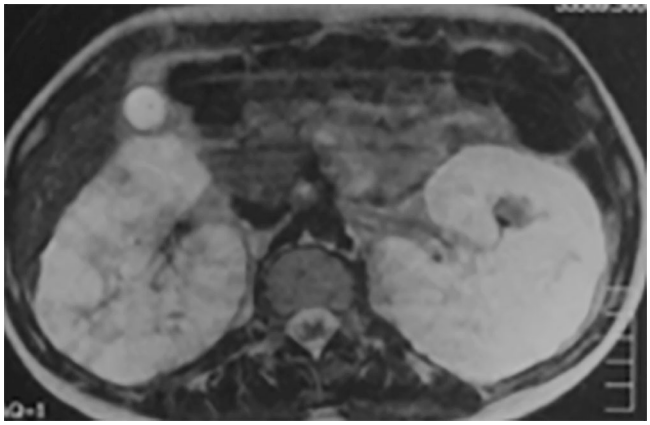

Fig. 12. ARPKD in a neonate. Axial T2-weighted MR image demonstrates markedly enlarged bilateral kidneys with increased T2 signal and loss of corticomedullary differentiation. Note no discrete cysts in the kidneys are delineated.

adults, the imaging findings of hepatic fibrosis with evidence of portal hypertension (splenomegaly, varices, and ascites) and nonobstructive saccular dilatation of the intrahepatic ducts (Caroli syndrome) can be seen along with renal cystic abnormalities (predominantly collecting duct ectasia typically extending to the cortex) (Fig. 13). Molecular diagnostics by mutation screening for the *PKHD1* gene can confirm the diagnosis and enable preimplantation and prenatal genetic screening in future pregnancies.

Treatment depends on the patient's presentation. In early life, artificial ventilation or resuscitation may be needed, and other treatment includes unilateral or bilateral nephrectomies, hypertension or infection control, splenectomy, dialysis, and renal transplant.

Autosomal-dominant tubulointerstitial kidney disease (ADTKD) (also called medullary cystic kidney disease [MCKD])

Clinical and genetic description

The Kidney Disease: Improving Global Outcomes (KDIGO) proposed a new terminology for this group of diseases, autosomal-dominant tubulointerstitial kidney disease (ADTKD), which refers to nonglomerular autosomal-dominant kidney diseases characterized by progressive tubulointerstitial fibrosis and progression to ESRD. The previously called MCKD1 is now called as ADTKD-MUC1 and the previously called MCKD2 is now called as ADTKD-UMOD [23]. It also includes the previously called 'familial juvenile hyperuricemic nephropathy type 2 (FJHN2)' and 'maturity-onset diabetes mellitus of the young type 5 (MODY5)'/'renal cyst and diabetes syndrome (RCAD)' [23], which are now called ADTKD-REN and ADTKD HNF1B, respectively, depending on the disease gene involved. ADTKD-MUC1 (MCKD1) has a defect in *MUC1* gene that is located on chromosome 1q21 that encodes mucin-1, whereas ADTKD-UMOD (MCKD2) has a defect in the *UMOD* gene that is on chromosome 16p12 and encodes uromodulin/Tamm-Horsfall mucoprotein.

The clinical and laboratory findings as well as histological findings of ADTKD are largely nonspecific. Presentation in childhood is frequent in ADTKD-REN and ADTKD-HNF1B, but rare in ADTKD-UMOD. ADTKD-MUC1 often shows late-onset ESRD and never occurs in childhood. ADTKD-UMOD may present with early gout and hyperuricemia, and ADTKD-REN may express mild hypotension, hyperuricemia, and hyperkalemia.

Radiological description

Renal cysts are not pathognomonic in these entities and the medulla appears not to be a specific location for the occasionally observed cysts (Fig. 14) [23].

ADTKD-HNF1B is caused by mutation of *HNF1B* gene and produces maturity-onset diabetes mellitus of the young type 5 (MODY5), which is also called renal cyst and diabetes syndrome (RCAD). This is inherited as an autosomal-dominant trait; however, as 50 % of

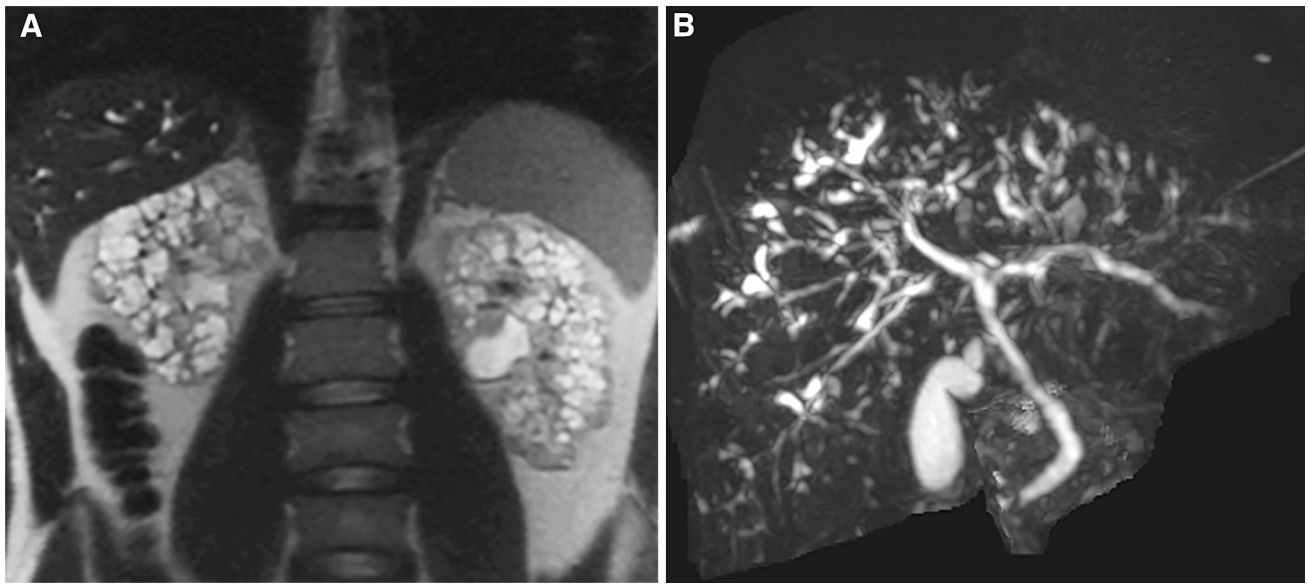

Fig. 13. ARPKD in adult in a 31-year-old male. **A** Coronal single-shot fast spin echo MR image demonstrates innumerable renal cysts in relatively normal-sized kidneys. **B** 3D MRCP image demonstrates multifocal fusiform dilatation of the intrahepatic ducts consistent with Caroli syndrome.

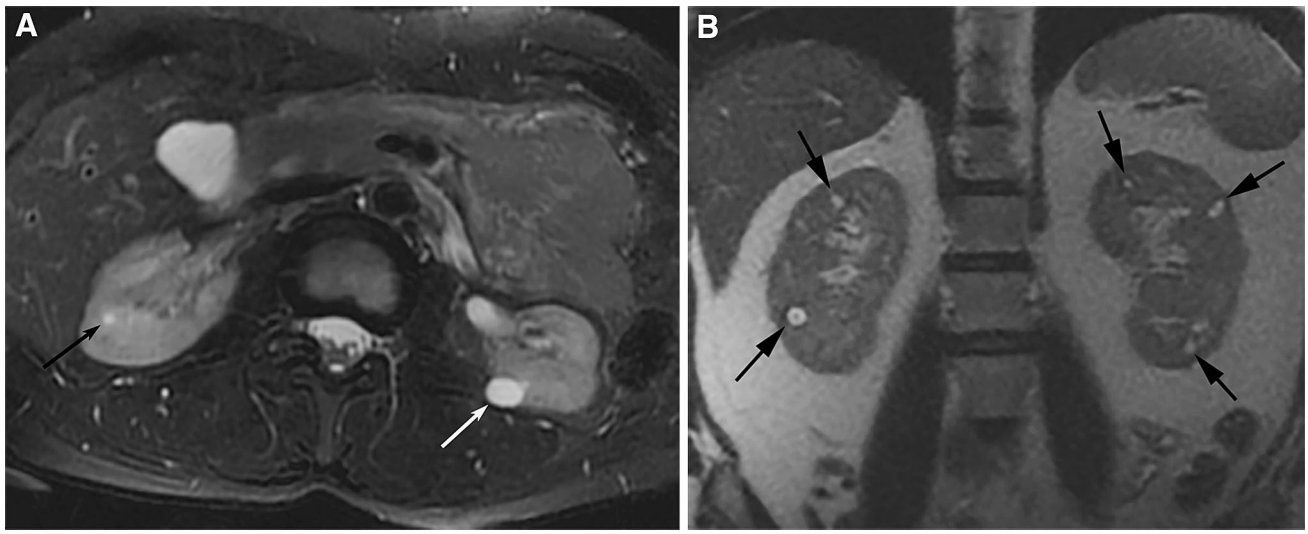

Fig. 14. ADTKD. **A** ADTKD-MUC1 in a 35-year-old female. Axial T2-weighted image demonstrates a tiny cyst in the medullary portion of the right kidney (*black arrow*) and a small cyst in the renal cortex of the left kidney (*white arrow*). **B** ADTKD-UMOD in a 42-year-old male. Coronal single-shot fast spin echo MR image demonstrates a few small cysts predominantly in the renal medullary regions or corticomedullary junctions (*arrows*).

mutations occur *de novo*, a family history is often absent. The *HNF1B* protein, HNF-1β, regulates tissue-specific gene expression in the kidney, liver, pancreas, and other epithelial organs [24]. Mutations to this gene often result in renal malformations including: renal cystic abnormalities including renal cysts, oligomeganephronia, familial juvenile hyperuricemic nephropathy, renal agenesis/hypoplasia, multicystic dysplastic kidney, and rarely renal failure. Other features include pancreatic hypoplasia, urinary tract dilatation, genital tract malformation (vaginal aplasia, rudimentary uterus, bicornuate uterus, cryptorchidism, epididymal cysts, and atresia of the vas deferens), abnormal liver function, and hypomagnesemia. The diagnosis is suggested in patients with MODY and renal malformation (41 % likelihood of *HNF1B* mutation) [25] (Fig. 15). A scoring system using multiple parameters for the diagnosis has been proposed [26].

Nephronophthisis (NPHP)

NPHP is a common genetic inherited disease causing ESRD in children and adolescents and is inherited as autosomal recessive trait. NPHP is genetically heterogeneous with mutations in at least 19 distinct genes identified but mutations in these genes account for only about one-half of the cases. The NPHP gene products are expressed in the primary cilia or centrosomes. The most common molecular cause of NPHP is deletion or mutation of the *NPHP1* gene, accounting for approximately 20 % of NPHP cases. The NPHP phenotype can be classified into three clinical forms, infantile, juvenile, and adolescent by the onset of ESRD (mean age of 1, 13, and 19 years, respectively) [20]. In the most common juvenile form, patients present with progressive tubular atrophy, small tubular cysts, and interstitial fibrosis leading to

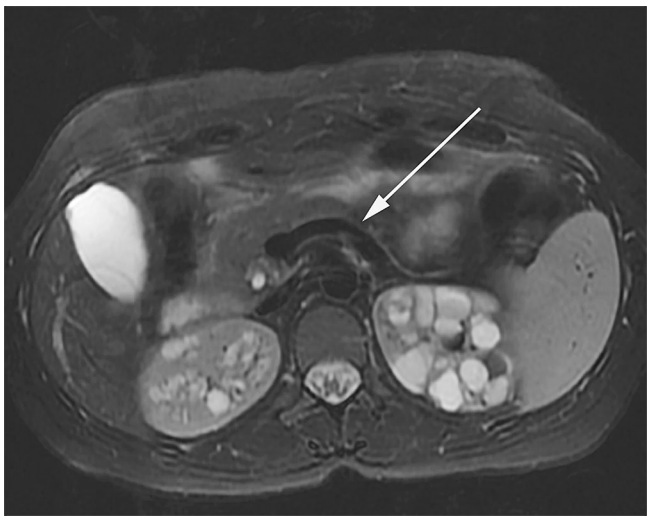

Fig. 15. ADTKD-HNF1B (renal cyst and diabetes syndrome) in a 35 year-old female. Axial T2-weighted MR image demonstrates multiple bilateral renal cysts. Note atrophic pancreatic body and tail (*arrow*). Although nonspecific, the diagnosis can be suggested when cystic renal disease is associated with maturity-onset diabetes mellitus and/or genital anomaly.

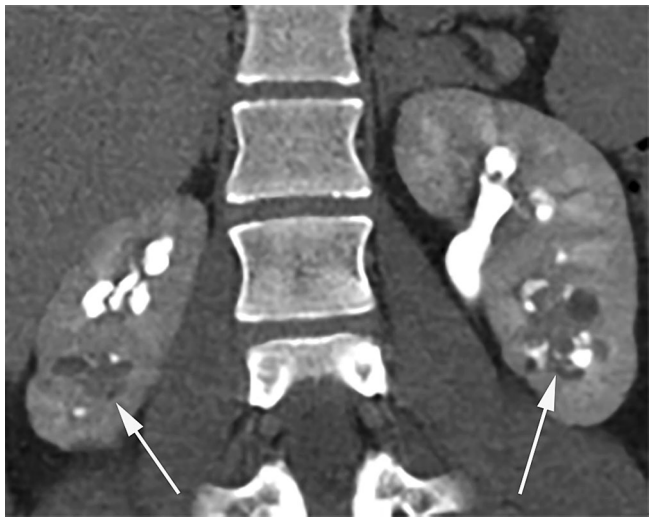

Fig. 17. Medullary sponge kidney in a 25-year-old female. Coronal reconstruction of excretory CT urogram demonstrates delayed contrast filling of the renal papillae predominantly in the upper kidneys. Note small cystic lesions (*arrows*) are seen in the medullary portions of the lower kidneys.

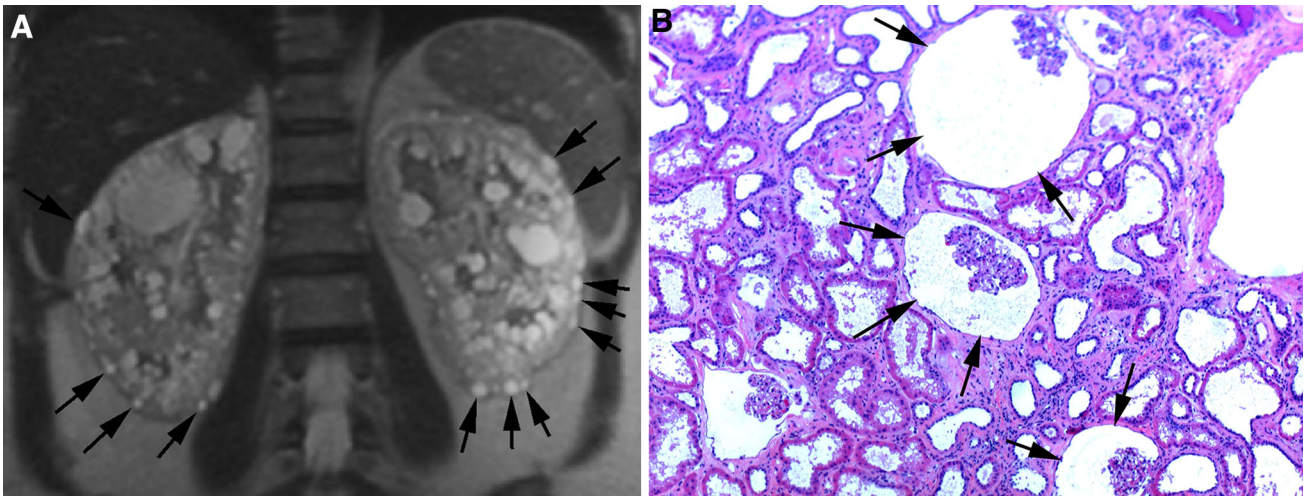

Fig. 16. Glomerulocystic kidney disease (GCKD) in a 59-year-old female with otherwise unknown cystic renal disease. **A** Coronal single-shot fast spin echo MR image demonstrates multiple renal cysts throughout the both kidneys. Note small cysts are located not only in the medullary portion but also in the cortex along the outer margin of the kidneys (*arrows*). Genetic testing was negative for PKD1 or PKD2 mutation. **B** Microphotograph (hematoxylin and eosin, ×100) shows dilated Bowman spaces or glomerular cysts (*arrows*) consistent with the diagnosis of GCKD. The GCKD is often diagnosed pathologically; however, genetically it is heterogeneous and may be associated with other hereditary diseases.

ESRD. The kidneys are characterized by hyperechogenicity and loss of corticomedullary differentiation on US and by a variable number of small cysts in the corticomedullary junction or medulla, best demonstrated by MRI but not always visible, and become progressively atrophic over time. The infantile form of NPHP combines features of NPHP with features of polycystic kidney disease (e.g., enlarged cystic kidneys).

NPHP can also be a feature of other-related autosomal recessive ciliopathies where it is associated with retinitis pigmentosa (Senior-Loken syndrome), cerebellar vermis aplasia, nystagmus and coloboma (Joubert syndrome), ocular motor apraxia (Cogan syndrome), liver fibrosis (Boichis syndrome), cone-shaped phalangeal epiphyses (Mainzer-Saldino syndrome), and short ribs (Jeune syndrome) [27]. Other syndromes included within the spectrum of NPHP-related ciliopathies include the perinatal lethal Meckel-Gruber syndrome (occipital encephalocele, polydactyly, microphthalmia, and liver fibrosis) and Bardet-Biedl syndrome (obesity, retinitis pigmentosa, polydactyly, and hypogenitalism).

Glomerulocystic kidney disease (GCKD)

Clinical and genetic description

GCKD are a heterogeneous group of diseases characterized by glomerular cysts that are often sporadic but occasionally familial (some reports suggest autosomal-dominant inheritance). Typically it occurs in children and young adult. Pathologically it is defined by a dilated Bowman space, greater than two times normal, and greater than 5 % of glomeruli involved. GCKD may be associated with other hereditary diseases such as early-onset ADPKD, late-onset ARPKD, ADTKD-UMOD, ADTKD-HNF1B, ADTKD-REN, TSC, or NPHP, or may be secondary to renal dysplasia, or ischemic GCKD.

Radiological description

The kidneys are slightly larger or normal in size. Imaging findings are variable in the fetus and neonate. In adults, multiple small renal cysts can be seen predominantly in the cortex, best seen on MRI (Fig. 16). Most patients progress to ESRD.

Medullary sponge kidney (MSK)

Clinical and genetic description

MSK is a benign condition characterized by tubular dilatation of the collecting ducts and cyst formation confined to the papillary portion of the medulla. It is associated with a high risk of developing urinary calcium stones. MSK is usually nonhereditary disease but autosomal-dominant inheritance in several families has been reported [28]. Most cases are asymptomatic but may be associated with microscopic or gross hematuria, stone formation, or infection. Incomplete distal renal tubular acidosis and/or hypercalciuria have been reported in up to 30–40 % of cases.

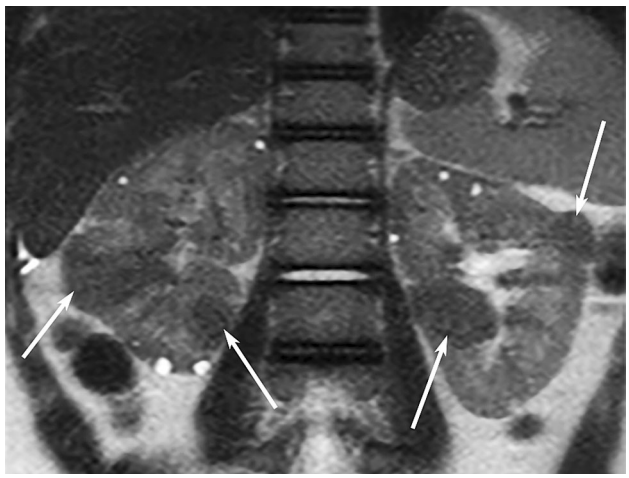

Fig. 18. Tuberous sclerosis complex in a 12-year-old male. Coronal half-Fourier acquisition single-shot turbo spin echo MR image demonstrates two low-signal masses (*arrows*) each kidney, consistent with angiomyolipomas. Multiple tiny cysts are also seen in both kidneys.

Radiological description

The kidneys are usually normal or slightly enlarged in size and the lesions are often bilateral (70 %). The dilated collecting ducts demonstrate typical paintbrush linear striations on excretory urography or CT urography, and may show clustered cysts in the papillary regions (Fig. 17). The affected patients usually have a good prognosis with normal life expectancy.

Renal cysts in hereditary tumor-related syndromes

Tuberous sclerosis complex (TSC)

Clinical and genetic description

TSC is an autosomal-dominant disease with an incidence of 1 in 6000. Two genes, *TSC1* and *TSC2*, were identified on the chromosome 9q34 and 16p13 and encode for hamartin and tuberin, respectively. The disease is often sporadic with high rates of spontaneous mutation (65–75 %), particularly with TSC2. Disease caused by *TSC1* mutation is often less severe than that by *TSC2* mutation. The hamartin-tuberin complex antagonizes an insulin signaling pathway that plays an important role in regulating cell size and number, and organ size. Mutations in tuberin or hamartin prevent the formation of the tuberin-hamartin complexes and activate mTOR [2].

TSC is characterized by hamartomatous proliferative lesions in many organs, including the skin, brain, retina,

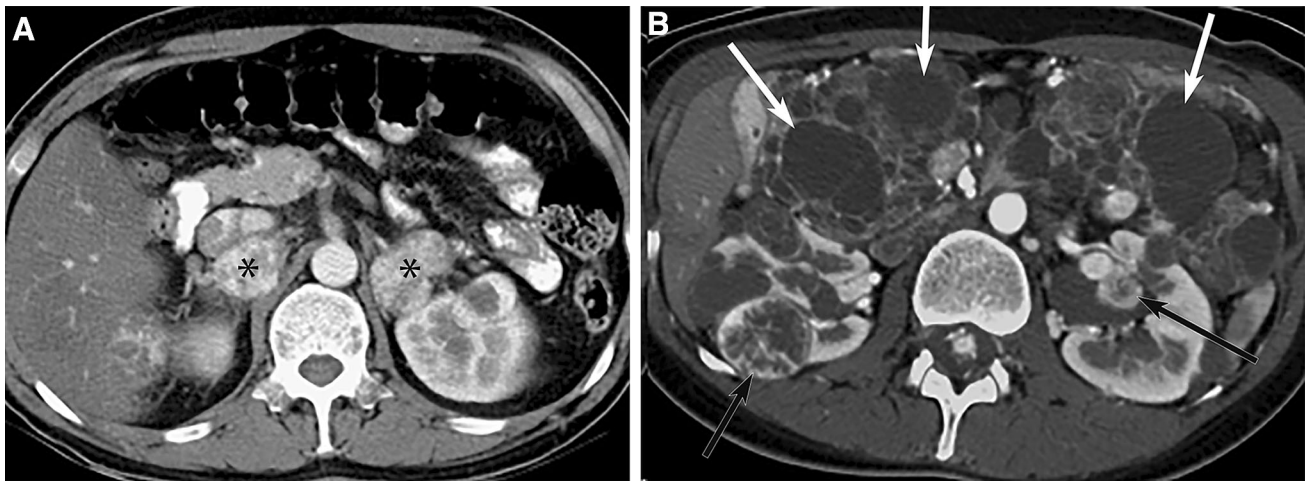

Fig. 19. von Hippel–Lindau disease in a 21-year-old female. **A**, **B** Two axial contrast-enhanced CT images demonstrate bilateral renal cysts and solid tumors (*black arrows*) as well as solid adrenal masses (*asterisks*) and multiple pancreatic cysts (*white arrows*).

Table 3. Clinical diagnostic criteria of tuberous sclerosis complex [29]

Major features
Hypomelanotic macules (≥3, at least 5-mm diameter)
Angiofibromas (≥3) or fibrous cephalic plaque
Ungual fibromas (≥2)
Shagreen patch
Multiple retinal hamartomas
Cortical dysplasias*
Subependymal nodules
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma
Lymphangioleiomyomatosis (LAM)†
Angiomyolipomas (≥2)†
Minor features
"Confetti" skin lesions
Dental enamel pits (>3)
Intraoral fibromas (≥2)
Retinal achromic patch
Multiple renal cysts
Nonrenal hamartomas

Definite diagnosis: two major features or one major feature with ≥2 minor features
Possible diagnosis: either one major feature or ≥2 minor features
* Includes tubers and cerebral white matter radial migration lines
† A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis

heart, endocrine glands, GI tract, lung, and kidneys. The 2012 International Tuberous Sclerosis Complex Consensus Group published diagnostic criteria which include 11 major features and six minor features (Table 3). Definite diagnosis can be made using two major features or one major with more than two minor features, and possible diagnosis can be made using either one major or more than two minor features [29]. Mutation screening of the two disease genes can confirm or determine the diagnosis.

Approximately 50 % of TSC patients show cystic renal disease and 2 % have the *TSC2/PKD1* contiguous gene syndrome. Renal involvement includes angiomyolipomas (70–80 %), cysts (47 %), oncocytomas, and clear cell RCCs (4 %). Angiomyolipomas are common in TSC (more frequent in TSC2), affect both genders (compared to female preponderance in general population), and are usually multiple and bilateral. Hemorrhage from angiomyolipoma is common, especially when the tumor reaches 4 cm in size. RCC in TSC is more common in female patients with a younger age, and often bilateral. It is usually clear cell type. Hypertension and renal failure may occur. Depending on the tumor size, nephron-sparing surgery, arterial embolization, ablation therapy, or bilateral nephrectomy can be performed. Clinical trials of mTOR inhibitors have been performed and found to be effective in managing tumor burden.

Radiological description

Diagnosis can be made using US, CT, or MRI by demonstrating fat within renal masses (Fig. 18). Non-fatty solid renal mass may represent fat-deficient angiomyolipoma, epithelioid angiomyolipoma, oncocytoma, or RCC.

von Hippel–Lindau syndrome (VHL)

Clinical and genetic description

VHL has an autosomal-dominant trait and occurs in 1 in 35,000. VHL is a tumor suppressor gene located on chromosome 3 (3p25-26). Inactivation of the *VHL* gene alleles causes uncontrolled cell growth, neoplastic transformation, and overexpression of VEGF in tumor cells and neoangiogenesis [30].

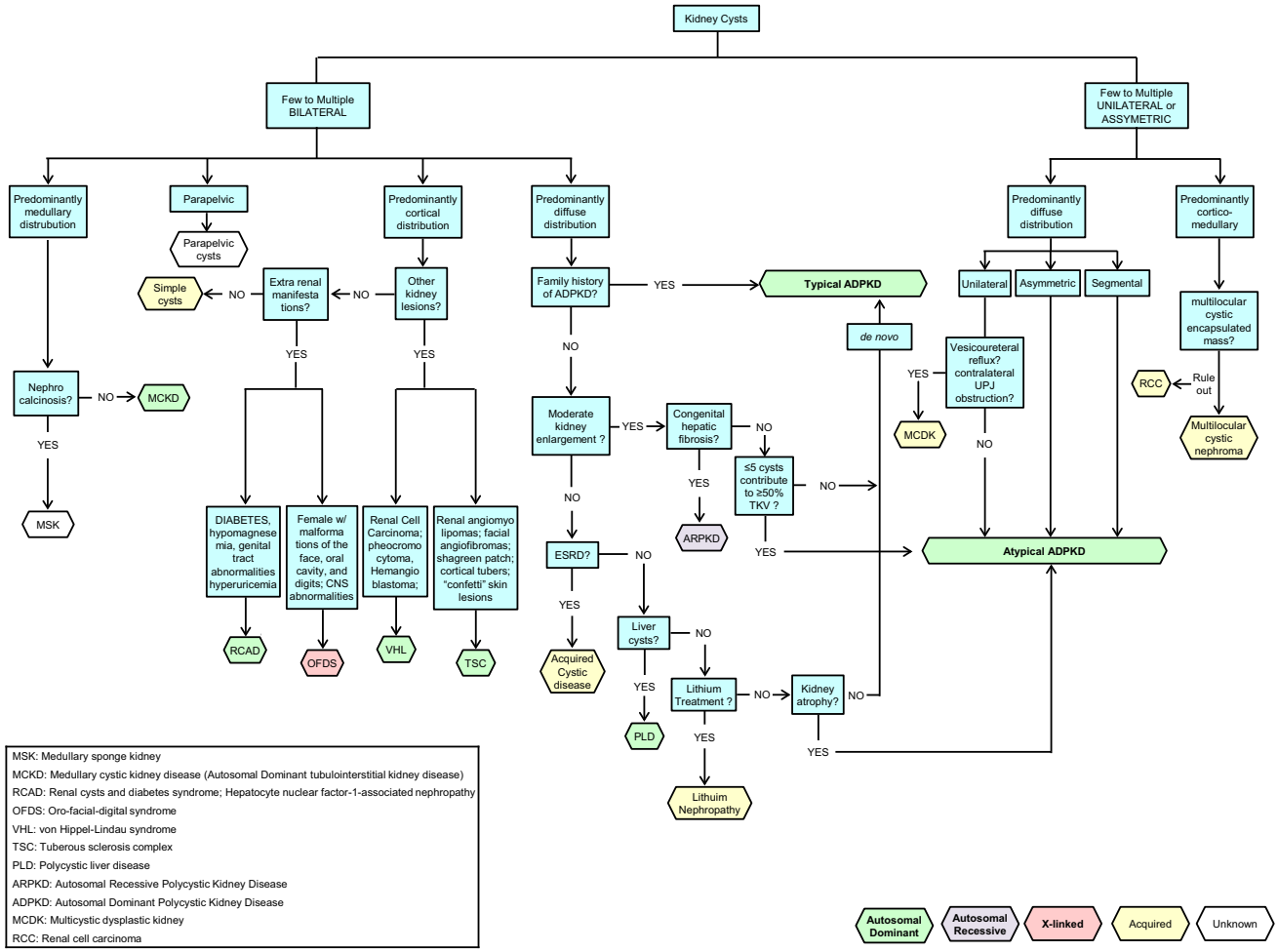

Fig. 20. Diagnostic algorithm of cystic renal disease.

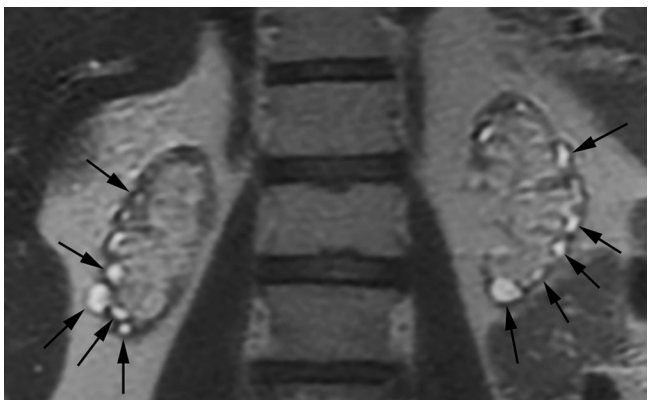

Fig. 21. Acquired cystic disease in a 57-year-old male. Small multiple cystic lesions are seen in bilateral severely atrophic kidneys in a patient with chronic renal failure and a history of dialysis. Patient now has a transplanted kidney in the pelvis (not shown).

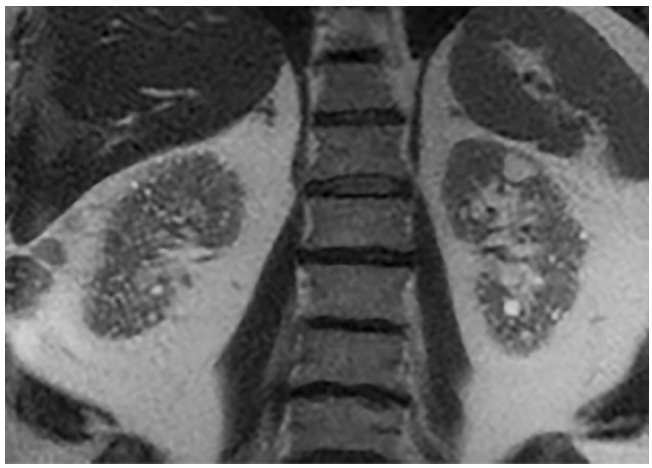

Fig. 22. Lithium nephrotoxicity in a 61-year-old female. Tiny innumerable bilateral renal cysts are seen throughout the renal cortices and medullas.

Cysts and benign and malignant tumors of various organs are seen, which include retinal hemangioma (50 %), endolymphatic sac tumors of the inner ear (10 %), cerebellar and spinal hemangioblastoma (21–72 %), pancreatic serous cystadenoma or neuroendocrine tumors, pheochromocytoma (7–20 %), clear cell RCC, epididymal, or broad ligament papillary cystadenoma.

Renal cysts (70 %) and pancreatic cysts (26 %) are common, whereas liver cysts are rare. RCC occurs in greater than 70 % during the lifetime and is the main cause of morbidity and mortality. RCCs occur early in life (mean age at 35 years) and are often multicentric and bilateral, with intracystic tumor nodules commonly seen.

VHL disease can be divided into type 1 (low risk for pheochromocytoma) and type 2 (high risk for pheochromocytoma) and type 2 disease is further divided into 2A (low risk for RCC), 2B (high risk for RCC), and 2C (pheochromocytoma only, no RCC or hemangioblastoma).

Radiological description

A diagnosis can be made by one characteristic tumor (hemangioblastoma, pheochromocytoma, or clear cell RCC) in the presence of a definitive family history, or two characteristic tumors (two or more CNS hemangioblastomas, or one hemangioblastoma and a visceral tumor) in the absence of a family history (Fig. 19). A molecular genetic diagnosis is helpful in evaluating VHL families, with the current mutation detection rate being almost 100 % [2].

Various imaging modalities including US, CT, MRI of the abdomen, MRI or CT of head and spine, PET or ^{131}I-MIBG scans are utilized for screening, diagnosis, and follow-up of the patients. As numerous serial imaging studies are needed in these patients, avoidance of ionizing radiation whenever possible, and dose reduction when CT or radiography is needed, should be considered. Nephron-sparing surgery, ablation therapy, bilateral nephrectomy and transplantation, or medical treatment including mTOR inhibitors can be used for treatment.

Differential diagnoses and diagnostic algorithm

Various nonhereditary conditions can be associated with sporadic, acquired, or neoplastic cystic renal diseases, the most common are simple renal cysts. These are rare in children but the incidence increases with age.

When cysts are bilateral and multiple, differentiation from hereditary disease may be difficult. In this case, the distribution of renal cysts can be helpful (Fig. 20). If they are diffusely distributed in both kidneys, ADPKD, ARPKD, acquired cystic renal disease, and lithium nephrotoxicity should be considered. Presence or absence of family history, renal enlargement, and associated liver disease can be helpful for further differentiation (Fig. 20). If the renal cysts are seen predominantly in the medullary regions, medullary cystic renal disease (ADTKD) and MSK should be considered, and if they are predominantly in the cortex, glomerulocystic disease can be considered. Acquired cystic renal disease can be seen in patients with ESRD, usually on dialysis. Typically small cystic lesions are seen in small atrophic kidneys (Fig. 21) and are associated with an increased risk for RCC. Lithium nephrotoxicity often presents with diabetes insipidus and on imaging innumerable tiny cysts are seen in both the cortex and medulla of normal- or small-sized kidneys (Fig. 22).

When the renal cysts are associated with solid or fatty masses, VHL and TSC should be considered, and when there are associated with extrarenal manifestation including diabetes, GU, facial, or CNS anomalies, RCAD (ADTKD-HNF1B) or oro-facial-digital syndrome can be considered (Fig. 21).

When the renal cysts are unilateral or asymmetric, the differential diagnoses may include multicystic dysplastic kidney, and benign and malignant cystic renal tumors including multilocular cystic nephroma and cystic RCC as well as atypical ADPKD and localized cystic disease. Localized cystic disease of the kidney refers to non-familial, non-progressive cystic renal disease, which involves the kidney partly, segmentally, or unilaterally [31]. It is often difficult to differentiate from atypical ADPKD or cystic neoplasm. Family history and genetic testing can be helpful in differentiating from atypical ADPKD.

Conclusion

Various genetic diseases are associated with renal cysts. Imaging is essential in the diagnosis, follow-up, and depiction of complications of inherited cystic renal disease. The renal size, location and distribution of renal cysts, and associated extrarenal disease are important to obtain a differential diagnosis.

Compliance with ethical standards

Conflict of interest None.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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