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Urogenital Imaging   REVIEW

Contemporary concepts and imaging findings in paediatric cystic kidney disease

Vasiliki Dermentzoglou, Virginia Grigoraki, Maria Zarifi

Department of Radiology, Agia Sophia Children's Hospital, Athens, Greece

ABSTRACT

The purpose of this article is to review the renal cystic diseases in children with regard to classification, genetic background, antenatal and postnatal ultrasonographic appearances and evolution of findings in childhood. Numerous classifications exist, even though the prevailing one divides cystic diseases in hereditary and non-hereditary. Contemporary data are continuously published for most of the sub-categories. Genetic mutations at the level of primary cilia are considered a causative factor for many renal cystic diseases which are now included in the spectrum of ciliopathies. Genetic mapping has documented gene mutations in cystic diseases that are generally considered non-hereditary, as well as in cystic tumours. Imaging plays an important role, as it helps to detect and characterise many of the cystic diseases based primarily on detailed sonographic analysis. Diagnosis can be achieved in many conditions during foetal life with ultrasound (US) and in selected cases with foetal magnetic resonance imaging (MRI). After birth, combined use of conventional and high-resolution US allows detailed definition of the extent and evolution of kidney manifestations. Appropriate monitoring with US seems crucial for patients' management. In selected cases (e.g. hepatobiliary disease, cystic tumours) primarily MRI and occasionally computed tomography (CT) are valuable diagnostic tools.

KEY WORDS	paediatric cystic kidney disease; ciliopathy; phacomatosis; hereditary cystic kidney disease; non-hereditary cystic kidney disease

CORRESPONDING AUTHOR, GUARANTOR	Corresponding author: Vasiliki Dermentzoglou, MD Department of Radiology, Agia Sophia Children's Hospital, 1 Thivon & Papadiamantopoulou Str., Athens 11527, Greece Email: vasderm71@gmail.com Guarantor: Maria Zarifi, MD, PhD Department of Radiology, Agia Sophia Children's Hospital, 1 Thivon & Papadiamantopoulou Str., Athens 11527, Greece Email: maria.zarifi@gmail.com

Introduction

"Cystic degeneration" of the kidneys was first described pathologically in 1841 and "polycystic kidneys" as a clinical syndrome in 1888. The heritable nature in some families was noted in 1899. Since then a great progress has taken place in the field of research and acquiring knowledge. The classification of renal cystic diseases in children in this review is based on the genetic or non-genetic origin [1]. Classification is currently reappraised, based on greater understanding of the developmental and genetic pathobiology of paediatric cystic kidney disease. A large group of hereditary renal cystic diseases are ciliopathies, that are genetic diseases with mutations affecting the formation and function of the cilia. This group includes classic diseases such as autosomal recessive and dominant polycystic kidney diseases and more recently recognised diseases, such as nephronophthisis-medullary cystic disease complex associated with ciliopathies and glomerulocystic kidney disease. Phakomatoses represent a distinct group of hereditary multisystem disorders whose pathobiology is related to mutations in genes that regulate tumour suppressor pathways and may have abdominal manifestations, including renal cystic lesions [2]. Among the non-hereditary cystic diseases are multicystic dysplastic kidney disease, medullary sponge kidney, simple renal cysts and secondary or acquired renal cysts. Cystic renal tumours are included, though new data focus on their association with gene mutations (DICER1 gene) [2]. **(Table 1)**.

Hereditary Diseases
The Ciliopathies

Ciliopathies are a group of clinically and genetically overlapping disorders whose aetiologies lie in defective cilia. Cilia are antenna-like sensory organelles that are present on the surface of nearly every cell in the body. They sense the extracellular environment and transduce signal back to the cells to facilitate their response. In this way they play essential roles affecting organ development and organ maintenance and repair. Defects in the structure and function of the primary cilia of renal tubular epithelial cells have been associated with the development of cysts in different forms of polycystic kidney disease. Ciliary disorders are caused by mutations of genes encoding ciliary proteins and affect multiple organs, including kidney, liver, pancreas, retina, central nervous system and skeletal system. The unifying molecular pathogenesis of this emerging class of disorders explains the overlap of abnormalities in different organ systems and links diseases of widely varied phaenotypes. It is important for radiologists to be able to recognise the multisystem manifestations of these syndromes, as imaging play an important role in the diagnosis and follow-up of affected patients [3-7].

1. Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is an inherited disease with an estimated frequency of 1:20.000 live births, caused by mutations in the PKHD1 (Polycystic Kidney Hepatic Disease 1) gene which is located on chromosome 6p12. Fibrocystin is the protein encoded by this gene, functioning on the primary cilia of renal and biliary epithelial cells. Cilia's dysfunction affects both kidneys and liver, promoting formation of ectatic renal collecting and biliary ducts, leading to renal and hepatic fibrosis. However, the relative severity of organ involvement is quite variable and the clinical manifestations of ARPKD differ considerably, with renal impairment representing the most common clinical feature [2, 8-10]. In severe cases, extensive involvement of the kidneys leads to oligohydramnios and pulmonary hypoplasia during the fetal period. The disease may be diagnosed in utero or during the perinatal period and the patients may die rapidly after birth due to severe respiratory distress [11, 12]. Other forms, with milder organ involvement, present during the first months of life with renal failure and portal hypertension and the patients may survive and progress satisfactorily through childhood as a consequence of better nephrological management. There is also a juvenile form that presents later in childhood with complications related primarily to liver disease (congenital hepatic fibrosis, CHF) [8, 10, 13].

In line with the variable clinical spectrum, the radiologic manifestations of ARPKD can also be variable. In neonates and infants with moderate to severe renal disease the kidneys are diffusely affected and appear markedly enlarged, even on foetal imaging or abdominal x-rays during the neonatal period. At US the kidneys are bulky and diffusely echogenic, with loss of corticomedullary differentiation because of the many

Table 1. Paediatric Cystic Kidney Diseases and discriminating features

	Cyst size and shape	Renal Size	Echogenicity of parenchyma (related to liver)	Corticomedullary differentiation	Position of cysts	Genes
HEREDITARY DISEASES						
The ciliopathies						
1. ARPKD	Multiple bilateral microscopic cysts, in some cases non discernible	Markedly enlarged	Diffusely increased	Lost	Medullary and cortical cysts, sparing of subcapsular area in some cases	PKHD1
2. ADPKD	Unilateral or bilateral cysts, increasing number and size with time	Initially normal, progressively may enlarge	Normal	Normal	Medullary and cortical cysts	PKD1, PKD2
3. Nephronophthisis, MCKD, nephronophthisis associated ciliopathies	Bilateral small discrete cysts	Initially normal and gradually decreasing	Increased	Poor	Medullary and corticomedullary cysts	NPHP genes/ MCKD genes/ genes related to syndromes
4. Glomerulocystic kidney Disease	Bilateral small cysts	Increased	Increased	Lost	Cortical and subcapsular cysts	PKD1,PKD2/ TCF2, genes related to syndromes
The phacomatoses						
1. Tuberous sclerosis	Multiple bilateral cysts of varying size and number, sometimes in combination with angiomyolipomas	Normal	Normal	Normal	Medullary and cortical cysts	TSC1, TSC2
2. Von Hippel-Lindau Syndrome	Simple or complex cysts	Normal	Normal	Normal	Medullary and cortical cysts	VHL

Table 1. Paediatric Cystic Kidney Diseases and discriminating features

NON HEREDITARY DISEASES

|	Cyst size and shape	Renal Size	Echogenicity of parenchyma (related to liver)	Corticomedullary differentiation	Position of cysts	Genes
1. Multicystic dysplastic kidney	Unilateral cysts of variable sizes and shapes in the area of the kidney	Become gradually smaller and in some cases disappear	Absent or dysplastic echogenic parenchyma	Absent	No recognisable pattern of distribution/hydronephrotic form with a large central cyst and small peripheral cysts	EYA1, SIX1, PAX2
2. Medullary sponge kidney	Non discernible cysts	Normal	Normal cortex, hyperechoic medulla, nephrolithiasis in some cases	Normal cortex, hyperechoic medulla	Medullar distribution because of dilated collecting ducts	GPNF
3. Simple renal cyst	More often solitary small or large, round or oval shaped cyst	Normal	Normal	Normal	Cortical cyst	-
4. Secondary or acquired renal cysts — Chronic renal failure, haemodialysis	Multiple bilateral small cysts	Decreased	Increased	Lost	Cortical and medullary cysts	-
4. Secondary or acquired renal cysts — Cystic renal dysplasia	Multiple small cysts	It depends on the dilatation of the collecting system	Increased	Poor	Cortical cysts	-
4. Secondary or acquired renal cysts — Paracalyceal diverticulum	Simple or complex cyst	Normal	Normal	Normal	Close to the renal pelvis	-
5. Cystic renal tumours	Unifocal multiseptated cystic mass	Increased because of the mass	Normal	Normal	Extension into the renal hilum	DICER 1
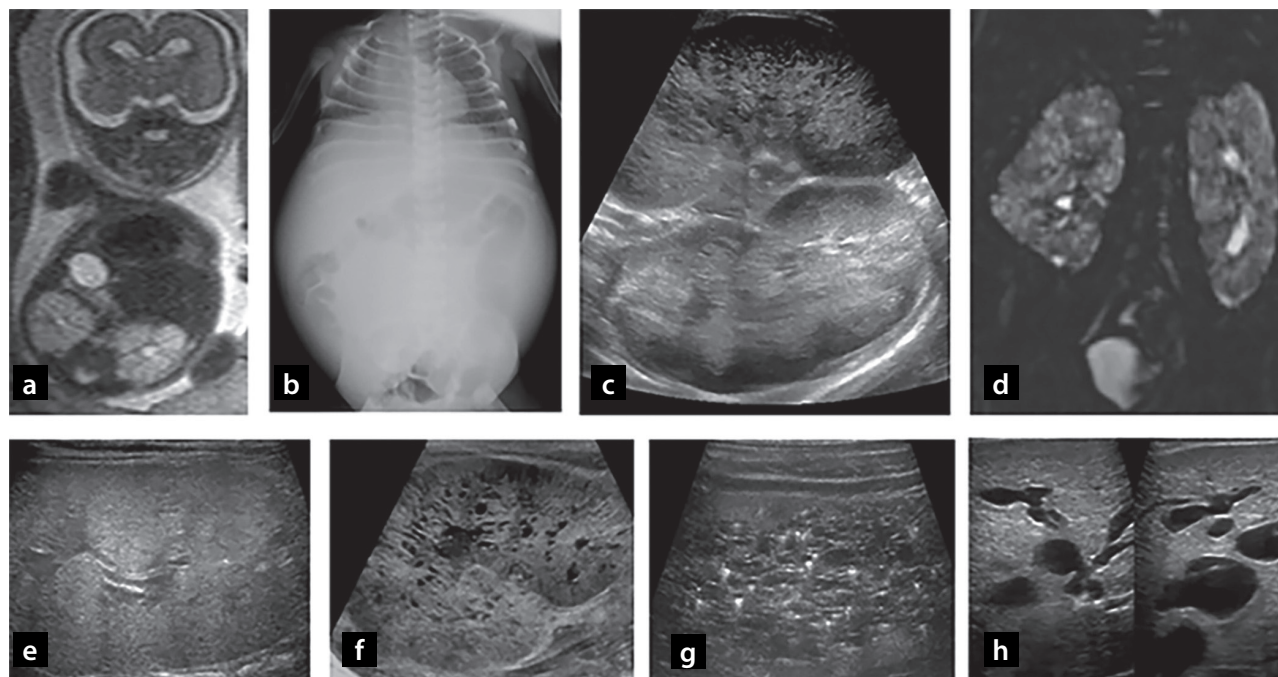
Fig. 1. ARPKD. **(a)** Foetal MRI at 21 weeks gestational age. Coronal T2W image, shows bilaterally enlarged hyperintense kidneys (Courtesy of Prof. Daniela Prayer, Vienna, Austria). **(b)** Anteroposterior x-ray of the chest and abdomen in a one-week male neonate depicts hypoplastic lungs and bulging flanks due to enlarged kidneys. **(c)** US coronal view of the abdomen in the same neonate confirms the marked nephromegaly with parenchymal thickening and hyperechoic medullary areas caused by numerous cysts. **(d)** Coronal T2W image shows hyperintense areas throughout both kidneys that represent dilated ducts. The next two images are longitudinal renal scans of different neonates: **(e)** diffusely increased echogenicity of the renal parenchyma and loss of corticomedullary differentiation. **(f)** numerous tiny microcysts in a radial distribution towards the cortical surface representing dilated tubules. **(g)** US image of a different pattern in an older child with ARPKD-CHF and renal failure shows hyperintense foci in the renal parenchyma that have developed with time. They may correspond to parenchymal deposits, like calcium precipitation secondary to diminished citrate excretion. **(h)** US image of the liver in the same child reveals Caroli disease with extensive cystic biliary dilatation.

interfaces between numerous, not discernible, microscopic cysts. High resolution US with linear-array transducer allows visualisation of numerous cylindrical cysts in the medulla and cortex that are oriented in a radial pattern representing dilated collecting ducts. A subcapsular area spared of cystic involvement has been described in some cases and represents an area that lacks collecting ducts. Macrocysts may be evident in a minority of cases. Cysts may increase in number and size during the course of the disease [14, 15]. Hepatic US may be normal in the newborn and young child. Abnormalities, when they become evident later during childhood, include hepatomegaly, increased liver echogenicity and dilated intrahepatic bile ducts (Caroli disease) **(Fig. 1)**. Renal US in patients presenting in childhood may depict almost normal-sized kidneys with more segmental involvement and less severe cystic appearance, while hepatic involvement is more prominent [8,16]. MRI may offer new perspective in assessing the progress of the disease and, besides enlarged kidneys, can demonstrate features related to hepatic fibrosis. Hepatomegaly, periportal high signal intensity and heterogeneous signal changes of the liver parenchyma may be seen on T2-weighted images while MRCP can demonstrate abnormalities of the intra- and extrahepatic bile ducts [2, 8].

2. Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD represents one of the most common inherited kidney diseases, occurring at an incidence of 1:400 to 1:1,000 live births. It is caused by a mutation in either of two
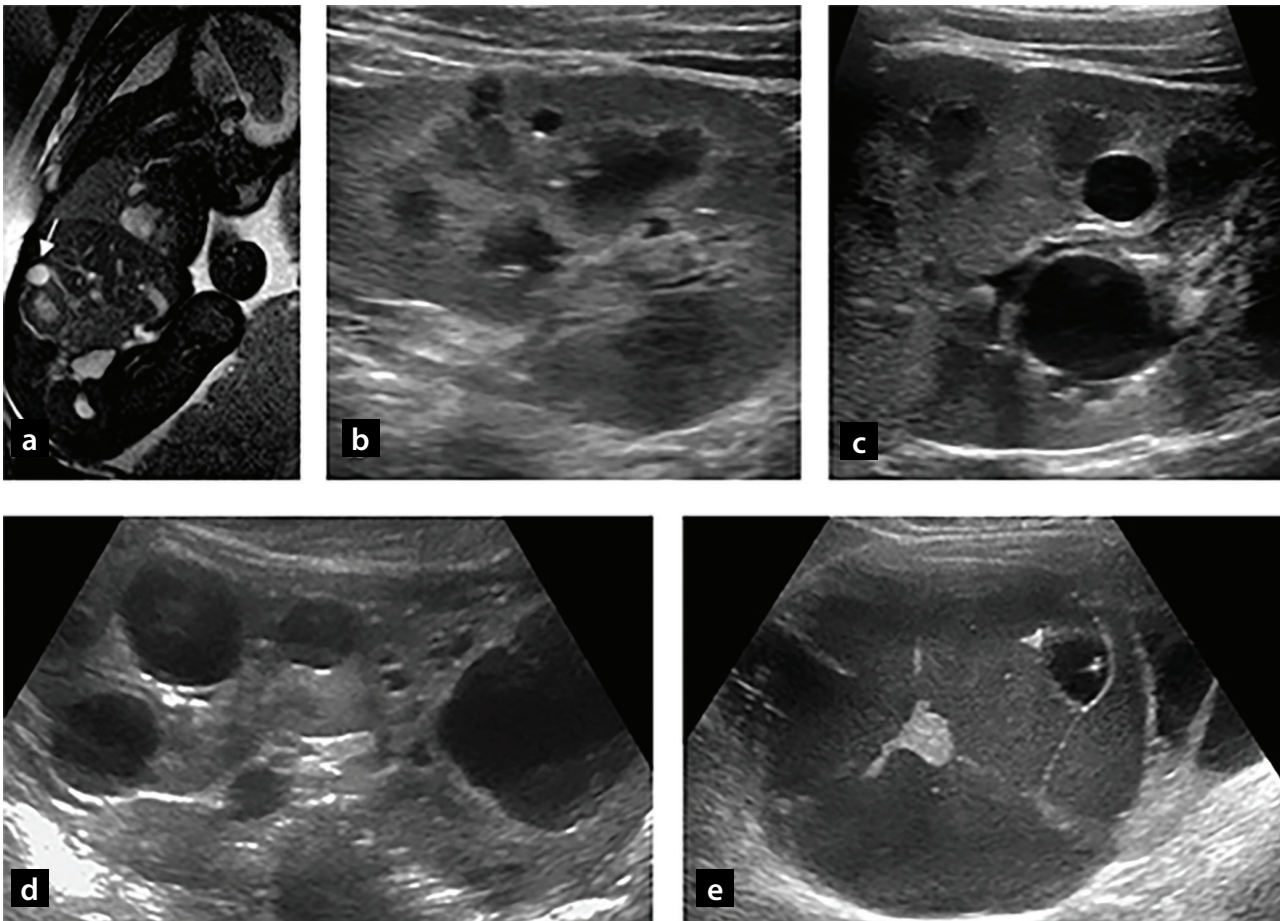
Fig. 2. *ADPKD.* **(a)** *Foetal MRI at 28 weeks gestational age. Sagittal T2W image shows a renal cystic lesion (arrow) in the foetus with family history of ADPKD (Courtesy of Prof. Daniela Prayer, Vienna, Austria). Different US images of kidneys in different cases of ADPKD show tiny cysts in* **(b)** *and multiple round bigger cysts in* **(c)** *and* **(d)**. **(e)** *US image in the contralateral kidney of the same case as* **(d)** *shows a large cyst complicated by haemorrhage with internal echoes and septa.*

genes, PKD1 and PKD2 (Polycystic Kidney Disease 1 & 2) that are located on chromosomes 16p and 4q respectively and code the proteins polycystin-1 and polycystin-2 [3]. These two proteins are localised in primary cilia of the epithelial cells lining the renal tubules. ADPKD is a ciliopathy related to abnormalities in renal tubule homeostasis in contrast to ARPKD where abnormalities of the renal tubular development are observed [8]. Most patients with AD-PKD are born with normal kidneys and are asymptomatic during childhood. Almost half of the cases appear in the first decade of life. Some of them are detected by chance and are proved by family screening. Haematuria, urinary tract infection, nephrolithiasis, hypertension and chronic kidney disease are common clinical manifestations in adulthood. Extrarenal manifestations typically include cysts in other organs, most commonly in the liver, and

cardiovascular complications, such as intracranial or aortic aneurysms [2, 8, 13].

US is the most common imaging modality used to diagnose ADPKD. The disease may be detected prenatally or during infancy as there is a subgroup with symptoms early in life that can sonographically confused with ARPKD [17, 18]. Two or more cysts, sometimes unilateral, in a child with positive family history are considered diagnostic. Later on, multiple round cysts of varying size with asymmetric distribution in the medulla and cortex of both kidneys represent the typical US finding. They range in size from microscopic to several centimeters in diameter, with varying amounts of normal renal parenchyma among them. With advancing age, increasing numbers of cysts replace renal parenchyma and the kidneys progressively enlarge, displacing adjacent organs in some cases [16, 17, 19, 20]. Cysts may
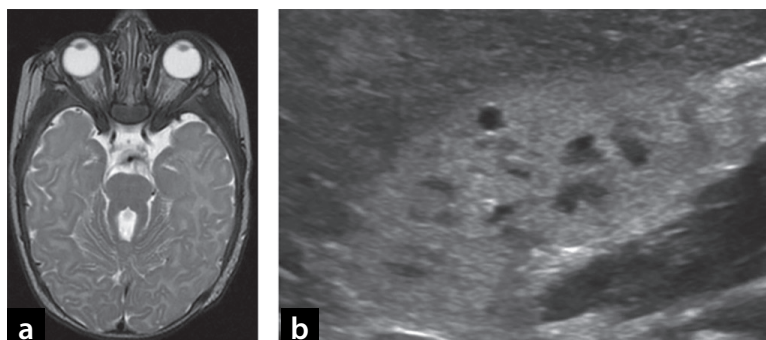
Fig. 3. *Joubert Syndrome. **(a)** Axial T2W MR image of a ten-year-old patient displays the typical "molar tooth sign" that results from thickened superior cerebellar peduncles coursing perpendicular to the brainstem **(b)** Longitudinal US image of the right kidney in the same patient shows small sized kidney with diffusely hyperechoic parenchyma and a small round cyst in the middle.*

become complicated by secondary haemorrhage or infection, necessitating in some cases further imaging with CT or MRI [2, 8] **(Fig. 2)**.

3. Nephronophthisis, Medullary Cystic Kidney Disease and nephronophthisis-associated ciliopathies

Nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD) are two clinically similar genetic diseases, which together are termed as "medullary cystic disease complex" (MCDC). They share almost the same histology as both are tubulointerstitial nephropathies. The term "nephronophthisis" is a Greek word meaning "disintegration of nephrons" which is one aspect of the histopathology. These hereditary diseases (NPHP-autosomal recessive and MCKD-autosomal dominant), are due to mutations in genes that encode nephrocystins and affect the primary cilia. They are genetically diverse, with abnormalities in 11 different genes (NPHP genes/MCKD genes) identified until today, that are responsible for a wide spectrum of phaenotypes. However, about 30% of the patients with nephronophthisis have an identifiable mutation. The identification of new genes will provide additional insight into the pathomechanism of nephronophthisis and how cilia are linked to cyst development [21-23].

Nephronophthisis spectrum is the most common genetic cause of end-stage renal disease in children and young adults. Presentation of NPHP may occur during infancy, but more typically in late childhood with polyuria, polydipsia, secondary enuresis, growth retardation and finally progressive renal failure. MCKD can occur in children, but generally presents later, in young adults, with similar clinical presentation.

Renal US at the initial stage of the disease shows normal-sized kidneys of increased echogenicity with poor corticomedullary differentiation and small discrete cysts,

which are medullary or corticomedullary in location. Imaging in a later stage reveals smaller, atrophic kidneys with increased echogenicity and more prominent cysts [2, 17, 19, 21].

Diagnosis is made by family history, renal biopsy or genetic testing. A molecular genetic analysis is currently the mainstay for making a definitive diagnosis of an NPHP ciliopathy [21].

Although certain nephronophthisis mutations primarily affect the kidneys, others cause significant extrarenal abnormalities, including retinal degeneration, situs abnormalities, hepatic fibrosis, central nervous system (CNS) and skeletal defects. A large variety of different syndromes have been published in association with NPHP and among them are Jeune syndrome (asphyxiated thoracic dystrophy/skeletal ciliopathy), Meckel-Gruber syndrome and Joubert syndrome (CNS ciliopathies). The extrarenal manifestations of these syndromes predominate over the renal disease and suggest the diagnosis [21, 22].

Meckel-Gruber syndrome is an autosomal recessive perinatally lethal disorder that classically includes cystic renal dysplasia related to dilated and dysplastic collecting ducts, polydactyly and occipital encephalocoele. Jeune syndrome is characterised by skeletal abnormalities (short thorax, short ribs, flared iliac wings) and visceral involvement (renal and pancreatic cysts, intrahepatic bile duct dilatation). Other skeletal ciliopathies are Ellis-van Creveld syndrome and orofacial syndrome type 1.

Joubert syndrome is an autosomal recessive disorder clinically characterised by hypotonia, cerebellar ataxia, classic facial features and mental retardation. The classic intracranial finding is the so-called molar tooth sign, characterised by horizontal orientation and thickening of the superior cerebellar peduncles. Eight causative gene mutations have been identified in patients with Joubert syndrome, all affecting cilia.
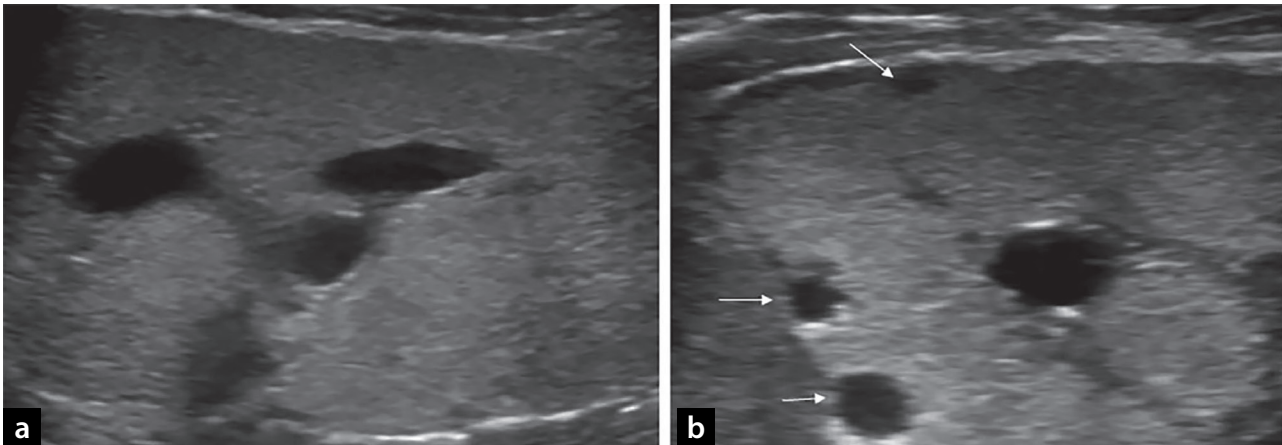
Fig. 4. Glomerulocystic kidney disease. **(a), (b)**: *US images of a newborn show enlarged echogenic kidneys with no corticomedullary differentiation and predominantly peripheral distribution of small cysts (arrows). There are no medullary cysts, which helps differentiation from ARPKD.*

Nephronophthisis is found in 17-27% of Joubert syndrome patients [8] **(Fig. 3)**.

The paediatric radiologist needs to consider these complex systemic diseases which are associated with disturbance of nephrogenesis for appropriate differential diagnosis and consultation of further diagnostic imaging and possible diagnostic testing.

4. Glomerulocystic kidney disease
Glomerulocystic kidney disease (GCKD) is not a single disease entity but rather has several forms, some of which are ciliopathies. It is characterised by predominance of cystic dilatation of the Bowman spaces around the glomeruli without significant tubular dilatation.

GCKD has been classified into three categories: 1. GCKD comprising nonsyndromal inheritable and sporadic forms of severely cystic kidneys in children and adults, 2. glomerulocystic kidneys associated with inheritable malformation syndromes and 3. glomerular cysts in dysplastic kidneys [24].

The first category refers to a rare congenital condition of newborns and young children that includes familial cases with autosomal dominant transmission and sporadic cases that are new mutations of the same disease. The autosomal dominant inheritance of GCKD has been associated with ADPKD genes (PKD1 and PKD2) but other genes are investigated too [25]. In the second category "glomerulocystic disease" is used as an anatomically descriptive term which his-

topathologically is associated with the presence of glomerular cysts. Some of the associated syndromes are tuberous sclerosis complex that is described later separately from ciliopathies, trisomy 13, Bardet Biedl syndrome, Zellweger's syndrome and maturity onset diabetes of the young [25]. The last syndrome is related to TCF2 gene that encodes hepatocyte nuclear factor-1β (HNF-1β). This is a protein that is critical for embryonic development of the kidney, pancreas, liver and Mullerian duct and the affected families exhibit a dual phaenotype that includes hypoplastic glomerulocystic kidney disease and early-onset diabetes [18, 19, 26].

The third category refers to acquired conditions and glomerulocystic disease can be seen as a component of renal dysplasia following significant renal damage. Therefore, glomerular cysts are sometimes present in multicystic dysplastic kidney or severe urinary tract stenosis. The glomerular cysts are a minor manifestation in comparison with the profound renal maldevelopment that is observed in these patients [27].

On US tiny cysts are visualised predominantly in the renal cortex and the subcapsular area. The kidneys may be grossly enlarged with generally increased echogenicity and loss of corticomedullary differentiation [15, 28] **(Fig 4)**. As diagnosis is made by family history, genetic mapping and histology, no additional imaging is helpful and US is used just for follow-up investigations.
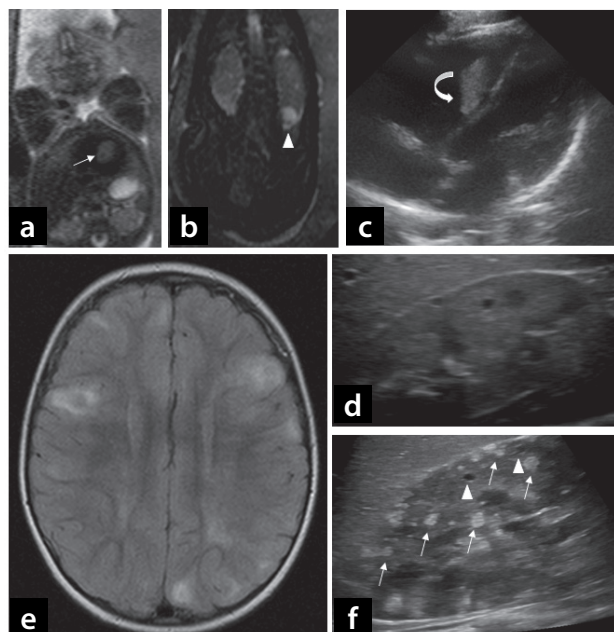
Fig. 5. *Tuberous sclerosis complex.* **(a)** *Foetal MRI at 28 weeks gestational age. Coronal T2W image reveals an intermediate signal intensity lesion of the heart (arrow), in combination with a cystic lesion of the kidney (arrowhead in **b**), findings indicative of tuberous sclerosis (Courtesy of Prof. Daniela Prayer, Vienna, Austria).* **(c)** *US image of the heart shows a hyperechoic lesion of the right ventricle in a neonate (curved arrow).* **(d)** *high resolution US image of the right kidney shows tiny microcysts, findings suggestive of tuberous sclerosis.* **(e)** *Axial Flair MR image of the brain of the same patient as **(c)** and **(d)** at a later age, reveals cortical tubers as hyperintense areas with subcortical distribution in both hemispheres.* **(f)** *US image of the kidney of another patient shows combination of multiple hyperechoic angiomyolipomas (arrows) and small in number and size cysts (arrowheads).*

A greater understanding of the developmental and genetic pathobiology of glomerulocystic disease will likely refine the classification system and may also reveal new therapeutic targets [25].

The Phacomatoses

The phakomatoses are a heterogeneous group of congenital neurocutaneous multisystem disorders that primary affect structures derived from the embryological neuroectoderm (CNS, eyes, skin). Nonectodermal involvement also occurs and abdominal manifestations, including renal cystic lesions, are common in these syndromes, especially in individuals with tuberous sclerosis and von Hippel-Lindau syndrome [2].

1. Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with an overall prevalence of 1 in 5,000-10,000 live births, being the second most common phakomatosis after neurofibromatosis 1. The disease is related to mutations in tumour suppressor genes TSC1 and TSC2. TSC1 encodes a protein called hamartin and TSC2 encodes a protein called tuberin. Tuberous sclerosis is characterised by the multisystemic development of tumours and numerous ectodermal (brain, skin) and mesodermal (kidney, heart, lung and bone) abnormalities, including hamartomatous lesions and cysts. In the kidneys, the primary mani-

festations are angiomyolipomas, cysts and rarely renal cell carcinoma. Cysts are generally bilateral and of varying size and number [2, 29]. TSC2 gene is located on chromosome 16 (16p13), very close to the gene PKD1 involved in the ADPKD. This vicinity explains one particular phaenotypic subgroup that is being increasingly recognised, the so-called "contiguous gene syndrome", and deserves a special mention. These patients have mutation that involves not only TSC2 but adjacent PKD1 as well, on chromosome 16. As such, these patients have a predominance of renal macrocysts relative to angiomyolipomas that are similar to the cyst in ADPKD and are at increased risk of renal insufficiency and hypertension later in life [30]. It is interesting that, although phacomatoses are not currently included in ciliopathies, new genetic researches reveal overlapping areas.

Clinically, tuberous sclerosis most commonly manifests with seizures and neurologic deficits. Brain lesions comprise cortical tubers which are scattered randomly over the cortical surface, subependymal nodules and giant cell astrocytomas. Other manifestations include characteristic skin lesions like adenoma sebaceum, retinal hamartomas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis, hepatic angiomyolipomas, pancreatic neuroendocrine tumours and vascular aneurysms and stenoses [2, 29, 30].
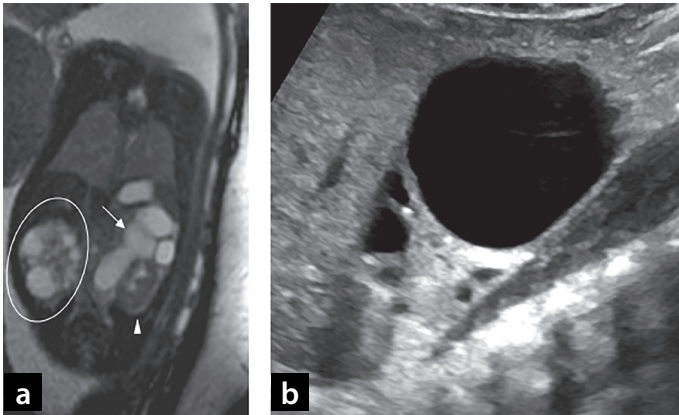
Renal involvement ranging from 40% to 50% is de-

Fig. 6. *Multicystic dysplastic kidney disease.* **(a)** *Foetal MRI reveals a combination of MCDK with anomaly of the contralateral kidney. Coronal T2W image displays multiple cysts of varying size displacing parenchyma of the kidney on the right (oval shape) while on the other side there is severe hydronephrosis of the upper pole moiety of a duplex kidney (arrow) and normal lower pole moiety (arrowhead) (Courtesy of Prof. Daniela Prayer, Vienna, Austria).* **(b)** *Longitudinal US image of the right kidney of a four-year-old boy shows MCKD with a large dominant cyst and smaller adjacent cysts that do not communicate with each other. There is no normal renal parenchyma among them.*

tected at a mean age of 6 years. It is the second most common cause of morbidity and mortality, following neurological manifestations. Angiomyolipomas are at a risk for haemorrhage, while cysts can compromise renal function if they enlarge and become numerous. They are encountered as isolated lesions or in combination. All patients with a presumptive diagnosis of TSC should undergo abdominal and cardiac US, as renal lesions and cardiac tumours may be the presenting manifestation, detected even during the foetal period. US is very useful for follow up of renal lesions while MRI of the brain is the gold standard method for CNS monitoring. CT and MRI are used to monitor abdominal manifestations as well [2, 30] **(Fig. 5)**.

2. Von Hippel-Lindau Syndrome

The von Hippel-Lindau (VHL) syndrome is an autosomal dominant disorder characterised by retinal angiomas and haemangioblastomaa of the cerebellum, brainstem and spinal cord. Phaeochromocytomas, liver haemangiomas, multiple pancreatic cysts, renal cysts and renal cell carcinoma may also occur. The responsible gene is a tumour suppressor gene located on chromosome 3 (3p25), whose normal function is to regulate cell growth.

Renal lesions are rarely detectable with imaging in children with VHL syndrome. Imaging may demonstrate simple or complex cysts, becoming more numerous with increasing patient age. Cystic lesions in this disease represent premalignant lesions and should be carefully observed [2, 31].

Non Hereditary Diseases

1. Multicystic Dysplastic Kidney Disease

Multicystic dysplastic kidney (MDKD) is one of the

most frequent cystic renal lesions in paediatric patients and a sporadic non-heritable developmental anomaly of the kidney. The incidence ranges from 1 in 1,000-4,300 live births and has a male predominance. It is one of the most commonly detected anomalies in prenatal imaging and the most common cause for an abdominal mass in neonates. There are two predominant theories regarding its aetiology. The first suggests that ureteral atresia leads to severe obstructive hydronephrosis and multicystic dysplastic kidney while the second proposes that an abnormal interaction between the ureteric bud and the metanephric blastema causes a failure of these structures to differentiate normally. Mutations in genes such as EYA1, SIX1 and PAX2, that are known to have important roles in ureteric bud development, have been identified in multiple human syndromes with renal dysplasia, including MCDK. Histologically, there are non-communicating cysts of various sizes, separated by tissue containing primitive dysplastic elements [32-35].

If MCDK is suspected on prenatal imaging, a postnatal US will confirm the diagnosis and screen for other urinary tract abnormalities **(Fig. 6)**. US demonstrates a mass of cysts of variable sizes and shapes with no recognisable pattern among absent or dysplastic, echogenic renal tissue components. Although there is a hydronephrotic form where there is a large central cyst and small peripherals cysts, it appears different from severe hydronephrosis where a central cystic structure that represents the renal pelvis communicates with peripheral dilated calices. About 20-50% of infants with one multicystic dysplastic kidney have a contralateral renal abnormality, such as vesicoureteral reflux, duplicated systems with ectop-

ic ureters or obstructed ureterocoeles and ureteropelvic junction obstruction, so additional imaging (voiding cystourethrogram, scintigraphy, MR urography) is proposed.

The natural history of MDKD is to become progressively smaller. Complete involution rates vary from 19-74% depending on different studies. Follow up US is suggested for screening of involution, compensatory hypertrophy of the contralateral kidney and for the risk of malignancy. As recent studies suggest that the risk of Wilms tumour may be even less than previously estimated, serial US follow up has been abandoned [36-38]. Renal US after birth, four weeks later, and at the age of two years, five years and ten years are a reasonable suggestion [32, 37].

2. Medullary sponge kidney

Medullary sponge kidney (MSK) is a benign disorder, rarely encountered in the paediatric population, characterised by dilatation of collecting tubules in the area of renal pyramids, affecting one or both kidneys. Although it is classified as a sporadic developmental anomaly, recent studies connect MSK with gene mutations (GDNF gene) and document it as part of conditions and syndromes such as Beckwith-Wiedemann syndrome and hemihypertrophy [39, 40]. Recent findings suggest that MSK may result from disruption of the ureteric bud-metanephric blastema interface that is critical in normal kidney development [41]. Ectasia and cystic malformation of the intrapyramidal collecting ducts creates microcysts containing concretions.

Patients with MSK are usually asymptomatic and kidneys may look sonographically normal in the early stages. Typical cases involve all renal papillae but MSK may be unilateral or may affect only a few papillae. Later patients may develop haematuria, renal colic or flank pain and US may reveal medullary nephrocalcinosis with hyperchoic patches of the medulla and papilla, or nephrolithiasis evident even on x-rays films. CT is performed in older patients and adults and may depict characteristic brushlike densities throughout multiple papillae of both kidneys on the excretory phase, consistent with renal tubular ectasia. Coexisting renal stones with ectatic tubules are diagnostic of medullary sponge kidney [42].

In patients with MSK and hemihypertrophy, serial

screening should be performed to exclude malignancies, including abdominal tumours [40].

3. Simple renal cyst

Although simple benign cysts are found in up to 50% of the population older than 50 years, they constitute a rare finding in children with an overall frequency of less than 1%. Histologically, they are unilocular, lined by a single layer of flattened epithelium and contain clear serous fluid. There is no communication between the cyst and the collecting system. The cysts arise in the renal cortex and are more often solitary rather than multiple. Most cysts are clinically silent and may be detected incidentally, but large ones can present as a palpable abdominal mass.

The classic sonographic findings include round or oval shaped cysts, thin walls and sharp margins, central anechoic fluid and posterior acoustic enhancement. Occasionally, simple cysts can be complicated by haemorrhage, infection or calcification. In these instances, sonography shows a complex mass with thick walls, internal echoes or septations. The possibility of underlying polycystic kidney disease is a concern in children with solitary renal cysts, therefore family investigation and follow-up are proposed [43-45].

4. Secondary or acquired renal cyst

Secondary cystic disease of the kidney occurs in a large percentage of patients during chronic renal failure and haemodialysis, even if the underlying disease is not cystic. The pathogenesis of this cyst formation is not clearly understood, but it is believed to be secondary to ischaemia or fibrosis. US shows small, echogenic kidneys containing multiple small cysts in both the cortex and the medulla. Increased incidence of malignancy, even in the wall of such cysts in end stage renal disease patients, necessitates frequent monitoring of the kidneys and surgical removal in selected cases.

Another category of acquired cysts is cystic renal dysplasia in the setting of congenital anomalies of the urinary tract, particularly obstruction. Ureteropelvic junction obstruction is the most common cause of upper urinary tract obstruction in children. Another cause is complete duplication of the renal collecting system and usually obstruction of the upper moiety of the duplicated kidney. US demonstrates the dilatation of the collecting system in
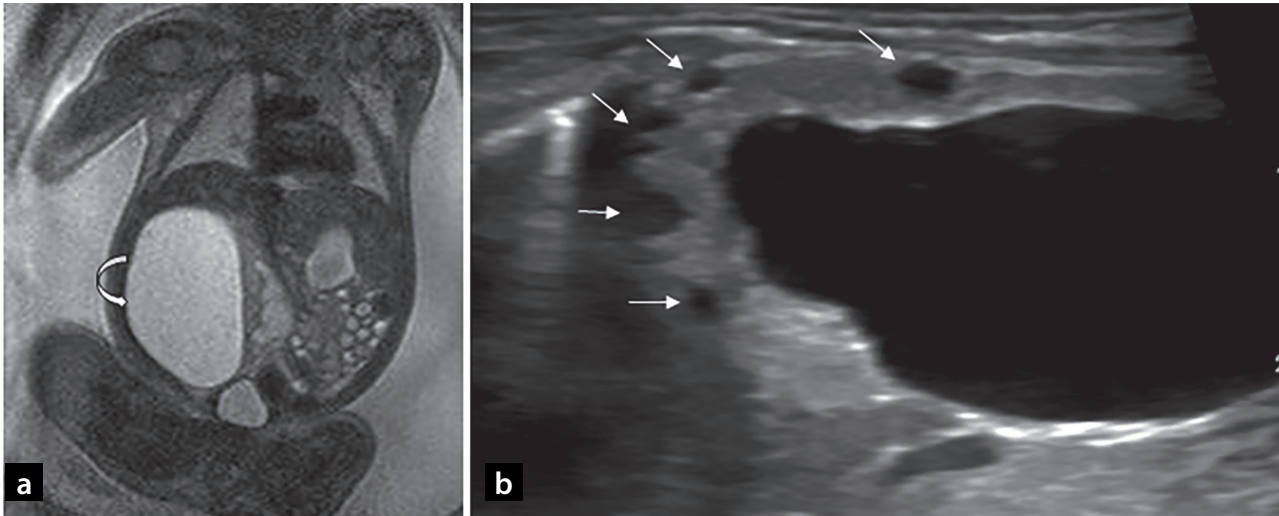
Fig. 7. *Acquired renal cysts.* **(a)** *Foetal MRI at 29 weeks gestational age. Coronal T2W image demonstrates a large urinoma (curved arrow) in a hydronephrotic kidney (Courtesy of Prof. Daniela Prayer, Vienna, Austria).* **(b)** *US image of a neonate with ureteropelvic stenosis shows thinned dysplastic hyperechoic parenchyma and multiple tiny cysts with peripheral distribution (arrows), findings indicative of cystic dysplasia.*

combination with hyperechoic renal parenchyma of varying thickness and small cysts visible with high resolution US in a peripheral distribution. Severe or chronic in utero obstruction has been associated with rupture of the collecting system, creating subcapsular urinomas and renal dysplasia with increased cortical echogenicity and cortical cysts (glomerular cysts) **(Fig. 7)**.

Paracalyceal diverticuli are another group of cysts which can be congenital or acquired and differentiation from other cysts may be difficult with US. Excretory phase MRI or CT are therefore necessary to disclose the contrast filling of the cyst and prove their communication with the collecting system.

5. Cystic renal tumours

Cystic renal tumours of the paediatric population include two histologically distinct but macroscopically indistinguishable lesions: cystic nephroma and cystic partially differentiated nephroblastoma (CPDN) [46]. They are recognised as neoplasms originating from metanephric tissue and are considered to represent part of a spectrum of differentiation that at the benign end is cystic nephroma and at the malignant end is nephroblastoma. CPDN lies in between [47]. Infants and young children aged from three months to four years are affected, and there is a 2:1 male predominance [46, 47]. Most patients present with an asymptomatic palpable abdominal mass. A relation of cystic nephroma

with the DICER1 gene mutation has recently been described. Individuals who have these mutations are specifically at increased risk of renal cystic nephromas, pleuropulmonary blastomas, ovarian stromal tumours, multinodular thyroid goiter and thyroid carcinoma, pituitary neoplasms and embryonal rhabdomyosarcoma [48, 49].

Cystic nephroma and CPDN are both unifocal completely cystic tumours with multiple septa and absence of solid components, ranging from 5 to 10 cm. The two tumours are distinguished microscopically by the cells found in the septa that are mature tubules in cystic nephroma and blastema cells in CPDN. The tumours appear as well circumscribed, encapsulated, multiseptated cystic masses with no nodular solid components. US may depict some flow in the septa, while contrast enhanced CT or MRI demonstrate capsule and septa enhancement. Cyst contents are usually anechoic on US, iso- or slightly attenuating relative to water on CT and with fluid signal intensity on MRI T2-W images [46, 47, 50]. It is a common feature of cystic nephromas to extend into the renal hilum [2] **(Fig. 8)**.

Cystic nephroma is typically cured by surgical resection alone. CPDN has the potential for more aggressive behaviour, although metastatic disease has not been reported.

Conclusion

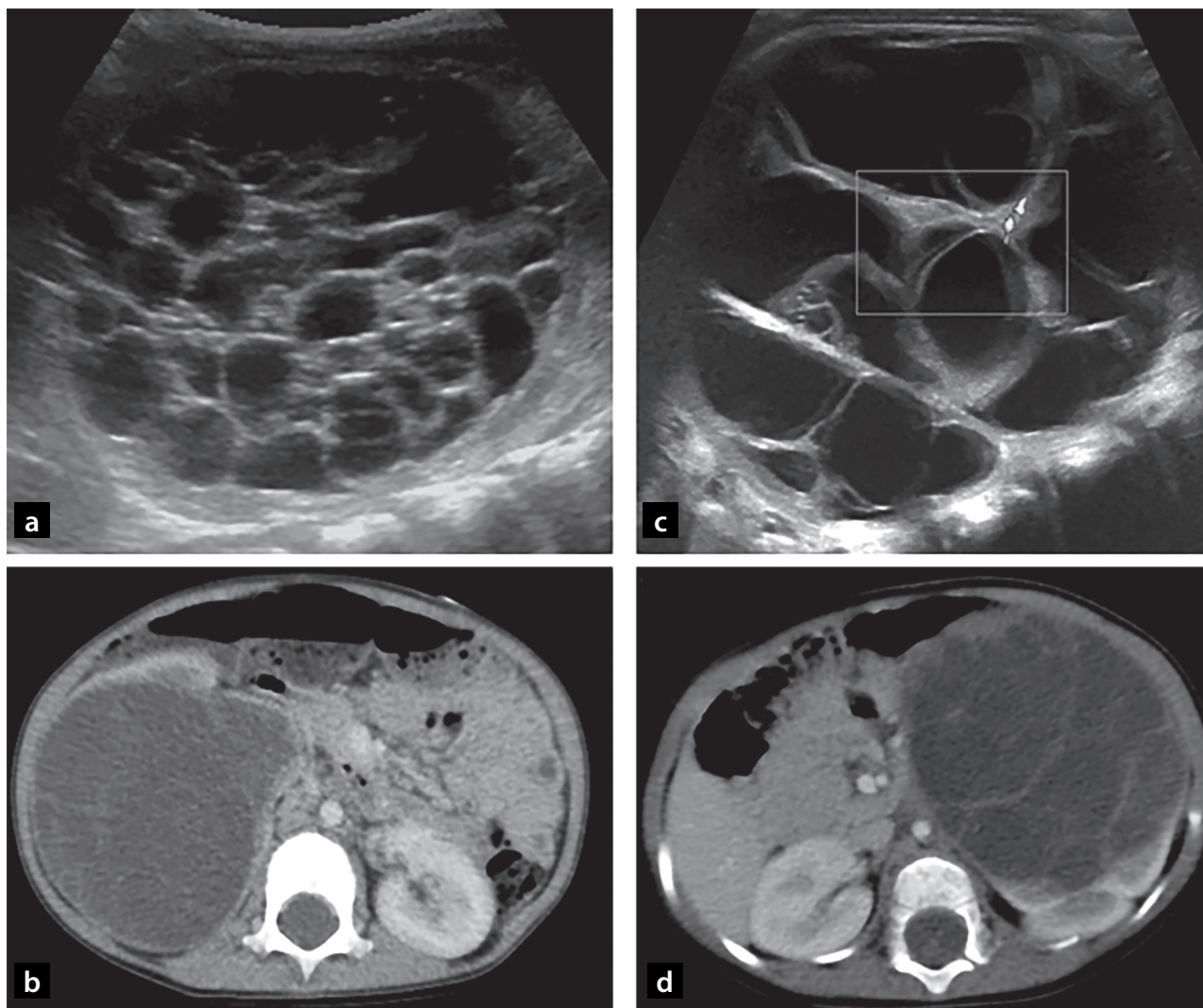Paediatric cystic renal disease includes a wide spec-

Fig. 8. *Cystic tumours.* **(a, b)**: *Cystic nephroma of the same child. US* **(a)** *shows a multiloculated mass with multiple internal septa replacing all of the left kidney. Contrast enhanced CT* **(b)** *confirms a water attenuation septated mass with mild enhancement of the septa.* **(c, d)**: *Cystic partially differentiated nephroblastoma. Colour Doppler US image* **(c)** *demonstrates a multiseptated mass with some flow within the septa and contrast enhanced CT* **(d)** *depicts the huge mass similar to cystic nephroma displacing renal parenchyma peripherally. It is obvious that these two tumours are indistinguishable by imaging.*

trum of hereditary and non-hereditary diseases. Imaging plays a crucial role from the foetal period through the entire paediatric age range. US is the first diagnostic tool and will guide further diagnostic work up with additional imaging studies or genetic testing. High resolution US with high frequency probes is particularly useful in assessing the size and distribution of minute cysts within the renal parenchyma. Knowledge of the different sonographic patterns is essential in order to correlate them with the clinical data, the familial history and in some cases suggest further ge-

netic investigation. Another role of sonography is to monitor the changing of US appearances of the kidneys with advancing age and to look for complications like cystic haemorrhage, renal lithiasis or portal hypertension. It is important for the radiologist to be familiar with the various disorders described in this article, in order to make a correct diagnosis which will contribute to positive patients' outcomes. **R**

Conflict of interest
The authors declared no conflicts of interest.

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