Renal Agenesis, Dysplasia, Hypoplasia, and Cystic Diseases of the Kidney

Christoph Mache and Holger Hubmann

Contents

C. Mache, MD (✉) • H. Hubmann, MD
Department of Paediatrics, Division of General
Paediatrics, Medical University Graz,
8036 Graz, Austria
e-mail: christoph.mache@medunigraz.at

1   Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) cover a wide range of structural malformations that result from defects in the morphogenesis of the kidney and/or urinary tract (see also chapter "Congenital Anomalies of the Renal Pelvis and Ureter"). CAKUT occur in approximately 1:500 live-born fetuses and are the most common cause of chronic kidney disease in children worldwide (Renkema et al. 2011; Vivante et al. 2014). Congenital anomalies of the kidney include renal agenesis, renal hypo-/dysplasia with or without cysts, and multicystic dysplastic kidneys (Weber 2012). While most CAKUT cases are sporadic, renal abnormalities are found in close relatives in approximately 10 % of cases (Winyard and Chitty 2008). Although CAKUT typically occur as isolated malformations, they occasionally develop in association with additional congenital anomalies outside the urinary tract, such as in the renal coloboma syndrome or the renal cysts and diabetes syndrome; they may also be associated with cardiac malformations. Currently, more than 20 monogenic CAKUT-causing genes have been identified, and recent findings suggest that CAKUT may arise from a multitude of different single-gene causes (Vivante et al. 2014). The malformation phenotypes vary from normally appearing kidneys with preserved renal function (i.e., incomplete

penetrance) to severe hypo-/dysplasia and end-stage renal disease. Features linked to worse prognosis are (1) bilateral disease, (2) decreased functional mass (which encompasses not just small kidneys but also large ones where cysts replace normal architecture), (3) lower urinary tract obstruction, and (4) anhydramnios or severe oligohydramnios (Winyard and Chitty 2008). Current management of CAKUT includes observation, surgical interventions, prophylaxis and treatment of urinary tract infections, strict blood pressure control, supplements for renal support, and nephroprotective treatment to slower the progression of chronic kidney disease.

Renal cysts are clinically and genetically heterogeneous conditions. Inherited cystic kidney disorders mainly include polycystic kidney diseases and entities comprising the nephronophthisis and medullary cystic kidney disease complex. These diseases are now categorized as ciliopathies – a disease concept characterized by dysfunction of the primary cilium, a hairlike cellular organelle (Hildebrandt et al. 2011). Cilia sense a wide variety of extracellular signals and transduce them into decisions regarding proliferation, polarity, nerve growth, differentiation, or tissue maintenance (Goetz and Anderson 2010). Since cilia are expressed in variable tissues, ciliopathies may affect multiple organs, and numerous pleiotropic human disorders have been attributed to defective cilia formation. It has become increasingly evident that many ciliopathies have a renal cystogenic component, making kidney cyst formation a hallmark feature of ciliopathies (Bergmann 2012). Renal dysplasia may as well occur as a result of defective differentiation during kidney development. Notably, cystic kidneys and renal dysplasia are important features of numerous genetic syndromes, such as the mainly recessively inherited ciliopathies Bardet-Biedl, Joubert, Meckel, and Jeune syndromes or the dominant disorders of tuberous sclerosis, von Hippel-Lindau disease, and branchio-oto-renal syndrome (Bergmann 2015). At present, treatment of ciliopathies still remains symptomatic.

Several medications are being investigated that might influence ciliary function and, for example, also may delay cyst formation and growth in the kidneys or will reduce the future extrarenal disease burden.

Details on imaging appearance and typical findings can be found in chapter "Imaging in Renal Agenesis, Dysplasia, Hypoplasia, and Cystic Diseases of the Kidney" which addresses all aspects of imaging including the respective imaging modalities, particularly focusing on ultrasonography (US) which is the most commonly used and often diagnostically sufficient modality in these entities.

> **Take Away**
> Congenital anomalies of the kidney are part of the CAKUT spectrum. Renal ciliopathies are frequently characterized by renal cyst formation; imaging heavily relies on US and is essential for initial evaluation and follow-up.

2 Renal Agenesis

Unilateral renal agenesis is characterized by the one-sided absence of renal tissue resulting from failure of embryonic kidney development (Woolf and Hillman 2007). The general incidence of unilateral renal agenesis has been estimated to be 1 in 2,000 (Westland et al. 2013). Renal agenesis occurs when the ureteric bud fails to form the ureter, renal pelvis, and renal mesenchyma that are necessary for the development of nephrons (Kerecuk et al. 2008). In these patients one frequently finds no ipsilateral ureter, as well as associated aplasia, hypoplasia, or anomalies of genital structures originating from the ipsilateral Wolffian and Mullerian ducts. Associated CAKUT have been identified in ~32 % of unilateral renal agenesis patients, the most common being vesicoureteric reflux (VUR) (24 %) (Westland et al. 2013). Extrarenal anomalies involving the gastrointestinal tract, heart, or musculoskeletal system were

reported in 31 % of patients. Injury of the solitary functioning kidney may lead to hypertension, microalbuminuria, and/or a decrease in glomerular filtration rate. Therefore, these patients need nephrological long-term follow-up, particularly in the absence of compensatory hypertrophy of the solitary kidney.

Bilateral renal agenesis occurs in 1 of 3,000 pregnancies and is considered almost uniformly fatal (Woodward et al. 2011). Affected fetuses die in utero from cord compression, or newborns die within hours after birth from severe pulmonary hypoplasia due to anhydramnios.

> **Take Away**
> In unilateral renal agenesis, sonographic evaluation and monitoring of the contralateral kidney are obligatory.

3 Renal Dysplasia and Hypoplasia

Dysplastic kidneys are abnormally developed kidneys with poorly branched or differentiated nephrons and collecting ducts, increased stroma, and, occasionally, cysts and metaplastic tissues, such as cartilage (Woolf et al. 2004). Dysplastic kidneys range in size from large distended kidneys with multiple large cysts to small kidneys with or without cysts (Rosenblum and Salomon 2008). They are common malformations affecting up to 1 in 1,000 of the general population and comprise part of the spectrum of CAKUT (Ichikawa et al. 2002). Renal dysplasia may be the only CAKUT manifestation or be associated with hydronephrosis, UPJO, megaureter, ureter duplex, VUR, and posterior urethral valve (Schedl 2007). Simple renal hypoplasia is defined as a small kidney with a reduced number of nephrons but maintained normal architecture. However, dysplastic features can be detected in most of these kidneys histologically as well (Watkins et al. 1997). As a consequence, a small kidney without cysts but with sonographical signs of dysplasia is often clinically referred to as a hypo-dysplastic kidney.

Apart from isolated cases of CAKUT, combined malformations with various extrarenal manifestations have been observed. More than 500 syndromes involving CAKUT have been described as yet (Weber 2012) (see also chapter "Genetics in Nephrourology"). However, until recently, only a little more than 20 monogenic CAKUT-causing genes have been identified (Vivante et al. 2014). Among them, autosomal dominant mutations in *HNF1ß* (renal cysts and diabetes syndrome), *PAX2* (renal coloboma syndrome) and *EYA1* (branchio-oto-renal syndrome) are the most important (Weber et al. 2006). Renal cysts and diabetes syndrome may include renal dysplasia, diabetes mellitus, hyperuricemia, hypomagnesemia, elevated liver function tests, and malformations of female internal genitalia (Ulinski et al. 2006; Adalat et al. 2009). Renal coloboma syndrome is characterized by coloboma of the optic nerve and renal dysplasia with/without VUR (Sanyanusin et al. 1995). Branchio-oto-renal syndrome is genetically heterogeneous and comprises variable combinations of anomalies of the kidneys, brachial arches (cysts or fistulae), and external and inner ear (deafness) (Chang et al. 2004).

> **Take Away**
> Nowadays, renal hypo dysplasia is mostly detected by fetal or postnatal US. Imaging of associated anomalies of the urinary tract as well as potential extrarenal malformations is important for a correct diagnosis as well as for adequate therapeutic decisions and follow-up.

4 Cystic Kidney Disease

4.1 Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is a recessively inherited ciliopathy caused by mutations of the *polycystic kidney and hepatic disease 1* gene (Bergmann et al. 2003). The incidence is approximately 1 in 20,000 live births. Its principal manifestations are polycystic

kidney disease and congenital hepatic fibrosis (Bergmann et al. 2005).

The majority of patients are severely affected and ARPKD is frequently detected in late pregnancy or at birth. Fetuses with ARPKD display massively enlarged kidneys and oligohydramnios due to fetal renal failure (see also chapter "Urogenital Fetal Imaging: US and MRI"). Approximately 30–50 % of affected neonates die shortly after birth from respiratory failure due to pulmonary hypoplasia and thoracic compression by the excessively enlarged kidneys. Those surviving the neonatal period frequently take a prolonged course and may develop end-stage renal failure in the second decade of life (Guay-Woodford and Desmond 2003). Moderately affected patients without perinatal manifestation may even enter adulthood with preserved renal function (Adeva et al. 2006).

While the early presentation of ARPKD is clearly dominated by renal disease and early-onset hypertension, liver disease with congenital hepatic fibrosis and biliary duct ectasia is also present in every ARPKD patient. The hepatobiliary complications may also dominate the clinical picture, particularly in older patients. Progressive hepatic fibrosis leads to portal hypertension causing hypersplenism with pancytopenia as well as esophageal varices with bleeding complications. ARPDK patients with extensive dilatations of intra- and extrahepatic bile ducts (Caroli's disease) are also at risk of ascending bacterial cholangitis (Kashtan et al. 1999).

> **Take Away**
> In ARPKD imaging should always include monitoring of congenital hepatic fibrosis and its potential complications.

4.2 Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is the most frequent life-threatening genetic disease (prevalence 1/500–1/1,000 live births) affecting approximately 12.5 million individuals worldwide (Harris and Torres 2009). About 50 % of ADPKD patients develop end-stage renal failure by the age of 60 years. While clinical symptoms usually only arise in adulthood, there is considerable phenotypic variability even within the same family. In children, diagnosis of ADPKD is frequently made by family screening or as an incidental finding on US. About 60 % of ADPKD children aged less than 5 years have already *one or more* renal cysts detectable by US (Gabow et al. 1997). In general, the finding of even one renal cyst should alert the physician to the possibility of ADPKD because simple cysts are otherwise rare in childhood. Therefore family history and investigation, in particular parental US, are obligatory. In children with parental ADPKD, the finding of one cyst can already be considered diagnostic (Ravine et al. 1994).

About 2 % of ADPKD patients manifest clinically before age 15 years (Bergmann 2012). ADPKD-related symptoms include arterial hypertension, pain, episodes of hematuria, renal calculi, proteinuria, infection, or a palpable mass. Risk factors for a more rapid progression of ADPKD are (1) renal enlargement early in life, (2) having more than ten renal cysts before age of 12 years, and (3) having blood pressures above the 75th percentile for age, height, and gender (Fick-Brosnahan et al. 2001). Occasional ADPKD cases are even associated with significant perinatal morbidity and mortality and may be indistinguishable from severe forms of ARPKD (Fick et al. 1993; Bergmann et al. 2011).

ADPKD is a systemic ciliopathy, and cysts may also arise in other organs, e.g., liver, pancreas, seminal vesicles, and arachnoid membrane (Torres et al. 2007). About 8 % of ADPKD patients develop intracranial aneurysms, particularly those with a positive family history for intracranial aneurysm and/or hemorrhage (Rossetti et al. 2003). Approximately 10 % of first aneurysmal ruptures were reported to occur before age 20 years (Chauveau et al. 1994). Cardiac valve disease, mainly mitral valve prolapse, has been detected in 26 % of ADPKD patients (Lumiaho et al. 2001).

4.3 Nephronophthisis (NPHP) and Medullary Cystic Kidney Disease (MCKD)

Nephronophthisis (NPHP) comprises a clinically and genetically heterogeneous group of autosomal recessive ciliopathies (Hildebrandt et al. 2011). NPHP is the most frequent genetic cause of end-stage renal disease during the first three decades of life (median age 13 years). Renal histopathology is characterized by the triad of (1) tubular basement disruption, (2) tubulointerstitial fibrosis with cell infiltration, and (3) tubular cysts, mainly at the corticomedullary junction (Waters and Beales 2011). Although NPHP is generally referred to as a cystic kidney disease, cysts are not an obligatory feature and frequently occur only after patients have progressed to end-stage renal failure. NPHP manifests clinically with a urinary concentration defect leading to polyuria and polydipsia, as well as anemia and progressive renal failure (Bergmann 2012). Since cilia are found in virtually all organs and serve distinct functions in different tissues, ciliopathies may cause a broad range of organ involvement. In NPHP extrarenal manifestations are frequent and bear a significant comorbidity (Waters and Beales 2011). Ciliopathies may involve the eyes (retinitis pigmentosa, oculomotor apraxia), the brain (cerebellar vermis hypo-/aplasia associated with the "molar tooth sign" on MRI, mental retardation, encephalocele), the liver (cholangiociliopathies with liver fibrosis), and the bones (short ribs, cone-shaped epiphyses, postaxial polydactyly). Based on the pattern of organ involvement, numerous syndromes with high phenotypic variability and considerable overlap have been described.

Take Away

In the majority of ADPKD patients, renal cysts arise already during childhood, and family history and parental US are mostly the key to diagnosis. Familial clustering of valvular heart disease and intracranial aneurysms must be taken in account.

MCKD is often considered the autosomal dominant variant of NPHP with a usually later onset of renal failure than in the recessive forms. Mutations in the gene encoding the ciliary protein uromodulin (Tamm-Horsfall glycoprotein) can lead to different tubulointerstitial nephropathies including MCKD2, glomerulocystic kidney disease, and familial juvenile hyperuricemic nephropathy (Vylet'al et al. 2006).

Take Away

In NPHP patients additional imaging of potential extrarenal manifestations involving, for example, the liver, brain, or bones, is essential for a correct and complete diagnosis as well as during follow-up.

4.4 Glomerulocystic Kidney Disease (GCKD)

GCKD is defined histologically by the occurrence of glomerular cysts with dilatation of the Bowman's space and glomerular tufts (Bernstein 1993). GCKD was described, e.g., in various ciliopathies including ADPKD (particularly in young infants), NPHP, and MCKD (type 2), as well as tuberous sclerosis and the renal cysts and diabetes syndrome (Mache et al. 2002). GCKD has also been associated with renal dysplasia and urinary tract obstruction (Bissler et al. 2010).

Take Away

GCKD is a histological finding in various cystic kidney diseases. Since in most of these patients no renal biopsy is performed, this diagnosis is rarely made and often missed, as there are no specific imaging or laboratory features that would suggest the diagnosis. However, this has no implication on treatment and prognosis.

4.5 Multicystic Dysplastic Kidney (MCDK)

Unilateral MCDK is the most common form of cystic renal dysplasia with an incidence of 1 in 2,200 to 1 in 4,300 live births (Schreuder et al. 2009). The ipsilateral ureter is frequently atretic and sometimes even absent, supporting the theory that MCDK results from early ureteral pathology during nephrogenesis (Woolf 1997). It usually affects the entire kidney, but rarely can also involve only a part of the kidney, e.g., in a duplex system (Jeon et al. 1999). Unilateral MCKD is commonly a sporadic malformation, incidental reports exist on MCDK in siblings, twins and families (Srivastava et al. 1999). Bilateral MCKD is usually incompatible with extrauterine life.

Renal function depends on the solitary functioning contralateral kidney. Abnormalities of the contralateral renal unit may be found in one-third of patients, mainly VUR (Schreuder et al. 2009). In the absence of compensatory hypertrophy, renal hypo-/dysplasia should be suspected. Injury of the solitary kidney may lead to hypertension, microalbuminuria, and/or a decrease in glomerular filtration rate. Furthermore, associated ipsilateral genital anomalies are found in up to 50 %, such as cystic dysplasia of the rete testis or the seminal vesicle. Previous concerns about an increased risk of hypertension and malignancy have been allayed based on results from longer follow-up studies and systematic reviews, as well as on some immature blastema found in surgery specimen that hypothetically allows for an increased risk of malignant differentiation later on (Narchi 2005a, b; Aslam et al. 2006).

Clinically, MCDK is commonly detected by fetal US. MCDK is now generally regarded as a benign condition with conservative management and long-term follow-up predominating over surgical removal. Nephrectomy is mostly restricted to cases with continuous growth leading to compression of adjacent structures, infection, hemorrhage, or suspected tumors. Spontaneous involution of MCKD was reported to be 35 % by 2 years, 47 % by 5 years, and 62 % by 10 years of age, respectively (Hayes et al. 2012). Larger postnatal MCDK (>5 cm) are less likely to involute already during the first decade of life than smaller MCDK (Hayes et al. 2012; Poggiali and Oliveira 2012).

> **Take Away**
> The task of imaging is to establish the diagnosis, to evaluate the contralateral renal unit, to detect rare complications, and to monitor the involution of MCKD.

4.6 Medullary Sponge Kidney (MSK)

MSK is a kidney malformation of unknown etiology that generally becomes manifest with nephrocalcinosis, recurrent renal stones, and pre-calyceal duct ectasias (erroneously diagnosed as cysts) (Fabris et al. 2013) (see also chapter "Urolithiasis and Nephrocalcinosis"). Clinically, MSK may present with renal colic, episodes of hematuria, pyelonephritis, or renal failure. Frequent findings are hypercalciuria as well as renal acidification and concentration defects. MSK rarely presents in childhood and may be a familial disease in up to 10 % of cases.

> **Take Away**
> In childhood MSK is a rare and mostly sporadic diagnosis suspected and established by the radiologist. Due to its probably heterogeneous etiology, a comprehensive nephrological work-up is mandatory.

4.7 Simple Renal Cyst

Simple renal cysts can occur spontaneously or be familial. They are rare in childhood with a reported incidence of 0.22 % (McHugh et al. 1991). Simple cysts do not bare any consequences or associated risks except for a few occasions, when growing cysts lead to hypertension, compression of adjacent structures, or obstruction of the collecting system (Churchill et al. 1975). In adults, cysts are much more common

(up to 50 %), and the development of simple renal cysts is seen as a normal aging phenomenon (Baert and Steg 1977; Tada et al. 1983).

Acquired cysts can occur in post-traumatic and post-inflammatory (tuberculous, etc.) settings or spontaneously develop in kidney parenchyma during chronic renal failure and on dialysis (Dunill et al. 1977; Leichter et al. 1988; Hogg 1992). As in end-stage kidneys with acquired cysts malignancy may develop, they need to be monitored (Bretan et al. 1986; Levine 1992).

Simple renal cysts are rare in infancy and childhood. US usually detects them as an incidental finding. Possible manifestation of a polycystic or dysplastic renal disease must be considered, and follow-up is warranted.

> **Take Away**
> In children, a renal cyst may be a feature of ADPKD or cystic renal dysplasia and always warrants at least a follow-up US examination.

4.8 Complicated Renal Cyst, Multiloculated Cyst, and Cystic Renal Tumor

"Complicated cyst" is a term coined by descriptive radiology. The exact definition varies depending on the imaging modality applied and the age of the patient. A complicated cyst is defined as a cystic lesion with some abnormalities, therefore not matching all criteria necessary for a simple cyst. These are small size, clear and sharp margins, no echoes or contents in the clear fluid, and no parenchymal rim or inclusion. The radiological changes of a complicated cyst may originate from secondary hemorrhage or sedimentation of proteins and of membrane cells. Calcifications may also occur, or infection may be present. Differentiation of these cysts, usually discovered by US, is essential and achieved in part by CT/MRI, in part in conjunction with clinical and laboratory findings (Table 1).

Table 1 Differential diagnosis of a complicated renal cyst

"Simple cyst" aggravated by:
Secondary hemorrhage
Sedimentation
Infection
Acquired cysts
Posttraumatic
Inflammatory cyst (abscess, tuberculoma)
Infected calyceal cyst with sedimentation and calculi
Partially thrombosed vascular aneurysm
Necrosis after infarction, abscess
Cystic malformation
Segmental MCDK
Dysplastic cysts
Multilocular cyst and multilocular cystic nephroma
Manifestation of polycystic kidney disease (particularly ADPKD)
Cystic renal tumor
Necrotic hamartoma, capillary hemangioma, vascular malformation, bleeding angiomyolipoma, and other cystic benign renal tumors
Cystic Wilms' tumor, cystic mesoblastic nephroma
Cystic carcinoma and other, partially necrotic or cystic, malignant renal tumors

This table lists the most important entities that have to be considered for differential diagnosis of complicated renal cysts

Tumors have to be recognized and imaged/treated appropriately. Many tumor entities can present as a cystic renal tumor; the histologies range from benign renal neoplasms to cystic Wilms' tumor, cystic mesoblastic nephroma, and cystic renal adenocarcinoma (Theissig et al. 1986; Babut et al. 1993; Upadhyay and Neely 1989). Definite diagnosis is often only made histologically as imaging features may not be characteristic in the individual case (see also chapter "Neoplasms of the Genitourinary System").

> **Take Away**
> If a renal cyst does not match the criteria of a "simple" cyst on US, further imaging modalities are necessary and determine whether a biopsy is taken or follow-up is scheduled.

Conclusion

Congenital anomalies of the kidney and cystic renal diseases comprise many entities that may be diagnostically challenging. Family history and investigation, clinical presentation and evolution, renal imaging, and searching for extrarenal manifestations are valuable diagnostic tools. In addition, next-generation sequencing-based approaches allow parallel analysis of multiple genes involved in nephrogenesis and ciliary function and increasingly provide accurate genetic diagnoses. An accurate diagnosis is essential for genetic counseling, prenatal diagnostics, and the clinical management of patients and their families.

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