# Congenital Upper Tract Anomalies: Duplication, Cystic Renal Dysplasia, Multicystic Dysplastic Kidney

10

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**Learning Objectives**

1. Explain the basic embryology of the kidneys and ureter and how that relates to pathologic conditions associated with duplication anomalies.
2. List the surgical options for managing duplication anomalies, ectopic ureteral insertion, ureterocele
3. Develop a comprehensive differential diagnosis for renal cysts in children.
4. What is the appropriate evaluation and investigations to consider for renal cysts in the pediatric population?

## 10.1 Introduction

A basic understanding of embryology is an important foundation for morphologic upper tract abnormalities. The embryologic development of the urinary tract occurs in several well-described stages [1]. In summary, there are three sets of nephric structures: the pronephros, mesonephros and metanephros. The pronephros is transient and regresses. The mesonephros is regulated by signals in the Wolffian duct and also regresses, although there is a functional component. The metanephros ultimately becomes the definitive kidney and development begins with the outgrowth of epithelial cells called the ureteric bud from the Wolffian duct. As the ureteric bud extends out from the mesonephric duct to reach the metanephric mesenchyme (metanephric blastema), signaling causes a critical branching cascade, which forms the elaborate collecting duct system.

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Reciprocal interactions between the ureteric bud and metanephric blastema explain much of the pathophysiology described within this chapter. The first branching interactions give rise to the major and minor calyces, into which the collecting ducts from the renal papillae drain. Branching problems can cause decreased kidney mass (hypoplasia) and defective structures (dysplasia). Alternatively, if the ureteric bud bifurcates or there are two distinct buds that arise from the mesonephric duct, partial or complete duplication of the kidney may result.

## 10.2 Renal Duplication

### 10.2.1 Scenario 1

A newborn infant is known antenatally to have a left duplex kidney with possible complete ureteric duplication. Postnatal VCUG is shown below (Fig. 10.1 a and b).

#### 10.2.1.1 Question 1

**What does this show and how can this be explained embryologically?**

#### 10.2.1.2 Answer 1

The VCUG shows reflux into both upper and lower moiety ureters on the left but no clubbing of the calyces. The urethra is not seen but from the limited views available, the bladder looks normal. There is suggestion of duplication on the right with reflux on the right.

**Embrylogy and Anatomy**

When multiple ureteric buds emerge from the developing Wolffian Duct, a variety of duplication anomalies can result, ranging from partial duplication, which may not be clinically significant, to complete duplication, representing two distinct collecting systems within the kidney and separate ureters inserting into the bladder. In >95% of cases, the anatomy follows the predictable Weigert-Meyer law [2, 3]. The upper and lower pole ureters cross prior to their respective insertions into the bladder. The lower pole moiety ureter enters the bladder at a lateral location relative to the upper pole moiety orifice. This leads to a shorter tunnel through the detrusor that is prone to reflux. The upper pole moiety ureter inserts more distally relative to the lower pole orifice, and more commonly results in an obstructive phenomenon, such as ureterocele. However, there is considerable variability in the possible pathology and it is possible for both poles to reflux, to drain normally, or for an ectopic location to obstruct. Consequently, while duplex kidneys may be normal, they are prone to dysplasia or progressive obstruction depending on the anatomy of their insertion at the level of the bladder. The more ectopic the ureteral orifice, the greater the likelihood of obstructing or refluxing pathology, and, consequently, associated dyplasia. When identified on voiding cystourethrogram, reflux into a lower pole presents in a pelvicalyceal pattern described as the “drooping lily” sign, with the lower pole calyces in a characteristic downward-deviating orientation.

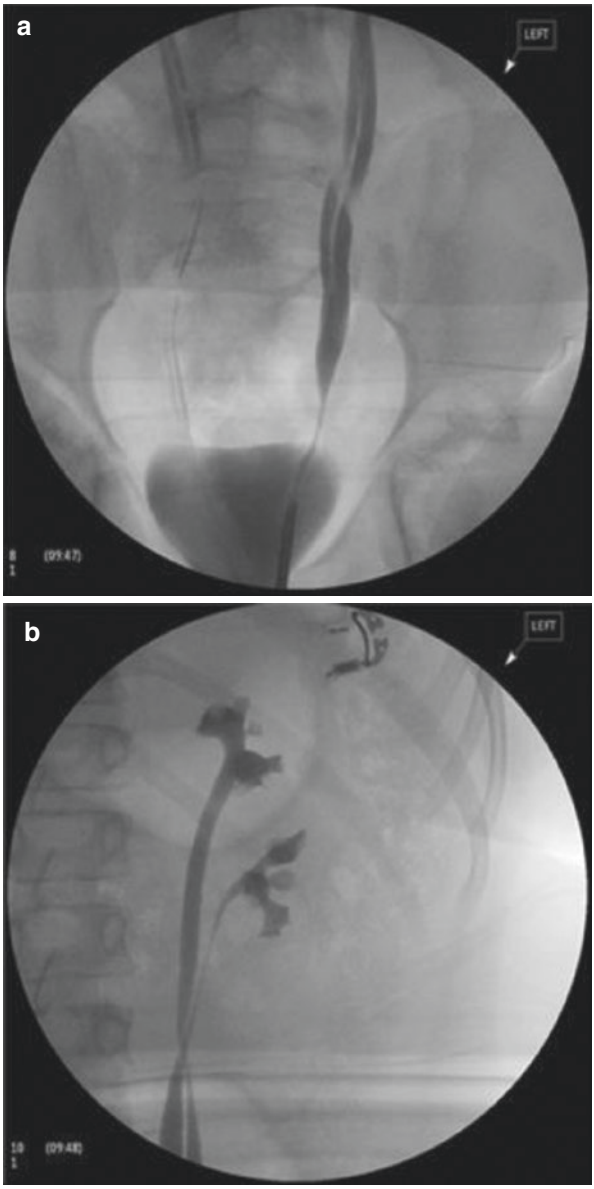


**Fig. 10.1** (**a** and **b**) Select voiding cystourethrogram images of the bladder and left upper tract

### Vesicoureteric Reflux in Duplex Kidneys

Due to the more lateral insertion site of the lower pole moiety orifice, reflux is a common finding, particularly in children presenting with UTI [4]. Repeated pyelonephritis in the setting of lower pole reflux may lead to a characteristic appearance of dysplasia or scarring limited to the lower moiety. It may also lead to hypertension and/or proteinuria. Pain should not be a presenting symptom of reflux.

#### 10.2.1.3 Question 2

**What would be your indications for surgical intervention in the above case?**

#### 10.2.1.4 Answer 2

Indications for surgical intervention in the setting of a refluxing duplex kidney are not different from a single system, and include prevention of recurrent UTIs, particularly febrile, and renal scarring. However, the natural history of reflux in duplex kidneys may not be as favorable. While lower grades of reflux may still resolve spontaneously, higher grades likely have a lower rate of resolution over time, which may prompt a more aggressive surgical decision [5].

#### 10.2.1.5 Question 3

**What are the surgical options if surgery is contemplated in duplex kidneys with reflux?**

#### 10.2.1.6 Answer 3

The traditional method of anti-reflux surgery for duplex systems is the common sheath reimplantation, where both the upper and lower pole moieties are mobilized and reimplanted together, regardless of the surgical technique [6]. Despite the additional degree of difficulty, success rates reportedly mirror traditional reimplantation outcomes. Of note, it is important to understand from a surgical perspective that the duplicated ureters share a common fascia as they course into the bladder, which includes a blood supply that would be compromised if separation were attempted. To avoid devascularization, the ureters should be reimplanted together, even if one of them does not reflux.

Endoscopic injection to treat reflux in duplex systems remains somewhat controversial. While many studies site a decreased success rate compared to single systems, the difference may not be statistically significant [7]. This choice likely remains very dependent on the bias of the surgeon and the shared-decision making goals of the family.

Lastly, there may be occasions when the lower pole of a duplex kidney is dyplastic and provides little function. If it continues to cause problems, while providing no benefit, a hemi-nephrectomy, either laparoscopic or open, is a reasonable option. Typically, the blood supply to a small, dyplastic pole is not robust and can be managed safely and easily. The goal is to remove as much of the associated ureter as possible, although leaving a short ureteral stump is rarely problematic [8].

#### 10.2.1.7 Question 4

**How can an ectopic ureteric insertion be explained embryologically and how can this be confirmed?**

#### 10.2.1.8 Answer 4

##### Ectopic Ureter in Duplex Kidneys

While ectopic ureteral insertion may occur in single system anatomy, the embryology of duplex systems encourages the upper pole moiety to insert more distally.

If the ureteral bud originates in an abnormally cranial position from the mesonephric duct, the distal ureter will migrate for a longer period along the path that the mesonephric duct follows before it is incorporated onto the bladder. If this position is too ectopic, it may not separate from the mesonephric duct at all and instead terminate in a mesonephric duct structure. In females, ectopic ureters may drain distal to the urinary sphincter into the vagina, which can result in continuous urinary incontinence. Asking parents if their girl seems to be constantly wet, or can be dry for distinct stretches of time can be revealing. Likewise, a careful examination of a girl with an ectopic ureter may identify continuous dripping of urine from the introitus. In males, a distal ectopic insertion may result in a ureter draining into a structure of the mesonephric duct, including the ejaculatory duct, seminal vesicle, vas deferens or epididymis. Although rare, the classic presentation is recurrent epididymo-orchitis.

Regardless of the patient sex, ectopic ureter leads to associated obstruction and resulting hydronephrosis. However, identifying the true orifice location can be challenging during cystoscopy or vaginoscopy. A variety of imaging studies can be used to help understand the anatomy. First, ultrasound is the most common screening tool to identify hydroureteronephrosis and perhaps an associated dysplastic appearing upper pole. However, it rarely can pinpoint the precise orifice location. Voiding cystourethrograms can be helpful, as ectopic ureters are frequently associated with reflux observed on. A ureteral orifice superior to the sphincter will demonstrate the reflux during filling, while a ureteral insertion below the sphincter commonly demonstrates reflux during the voiding phase. Lastly, CT and MRI imaging with delayed sequences may most accurately capture the precise anatomy of an ectopic insertion, however, these also represent the most time and cost intensive modalities.

#### 10.2.1.9 Question 5

**What are the management options for an ectopic ureteric insertion?**

#### 10.2.1.10 Answer 5

Ectopic ureteral insertion most commonly requires surgery. Most commonly, the associated upper pole is poorly functioning and requires upper pole hemi-nephrectomy. Similarly to the above-mentioned lower pole hemi-nephrectomy, retaining the distal ureteric stump is typically safe and may obviate the need for a more morbid complete ureterectomy [9]. In situations where there is upper pole function worth salvaging, alternatives to hemi-nephrectomy include reimplantation or uretero-ureterostomy depending on the surgeon's preference for a upper or lower tract reconstruction approach.

#### 10.2.1.11 Question 6

**What are the management options for a ureterocele associated with a duplex kidney?**

#### 10.2.1.12 Answer 6

**Ureterocele in Duplex Kidneys**

The risk of ureterocele is markedly higher in duplex kidneys compared to single systems, perhaps as high as 5–20% [4]. Antenatal sonography most commonly identifies hydronephrosis associated with the obstructive nature of ureteroceles, although UTI is also a possible presentation and distal ureteral stones can be observed in adult patients presenting with previously undiagnosed ureteroceles. In duplex kidneys, the ureterocele is almost always associated with the upper pole system, however, the size of the ureterocele may impact the bladder and other ureters more globally. The lower pole moiety may be obstructed by a markedly dilated upper pole ureter. Meanwhile, a cecoureterocele may obstruct the bladder outlet and affect the contralateral system as well. Finally, concurrent reflux to the ipsilateral lower pole system, and the contralateral kidney is significantly elevated [10]. It is beyond the scope of this chapter to describe all the various management options for ureterocele, and depends on the degree of obstruction, range of symptoms, and associated renal function. Options vary tremendously, from simple conservative observation, to endoscopic ureterocele puncture, to extirpative upper pole heminephrectomy, to complex reconstruction with ureterocele excision, bladder neck repair and re-implantation.

## 10.3 Cystic Renal Dysplasia

### 10.3.1 Overview

Renal cysts represent an enclosed, fluid-filled cavity that may develop in a tubular segment of the kidney. They represent an imbalance of secretory and absorptive properties of renal epithelial cells. Cystic disease may represent a wide spectrum of entities that are inheritable or sporadic, with each class representing benign and morbid conditions. Simple renal cysts, multilocular cyst (cystic nephroma), and acquired cystic renal disease represent some of the most significant sporadic conditions. Polycystic disease, Tuberous Sclerosis and von Hippel–Lindau disease are some of the most significant inheritable conditions. Finally, multicystic dysplastic kidney is a unique, non-inheritable entity.

### 10.3.2 Scenario 2

#### 10.3.2.1 Question 1

This child was noted to have an incidental finding in the left kidney on a CT scan (Fig. 10.2) done for other reasons. What does this show and is the finding significant? What would be your management?

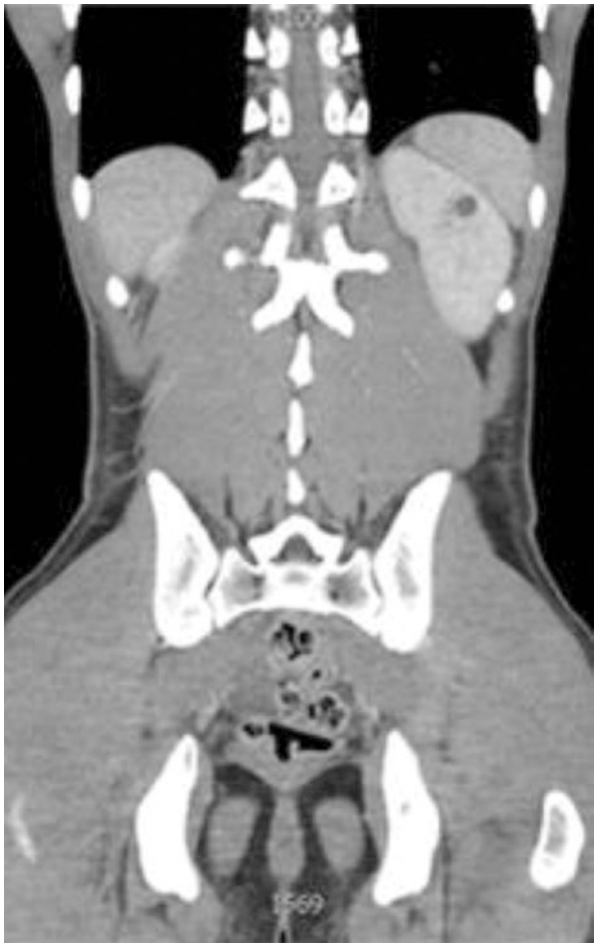

**Fig. 10.2** CT scan of the abdomen and pelvis with contrast (nephrogenic phase)

#### 10.3.2.2 Answer 1

The CT scan shows a simple renal cyst in the left kidney.

**Simple Renal Cysts**

Simple renal cysts are quite common in adults, but rarely found in children, thus commonly raising concern for more serious conditions. However, simple isolated renal cysts are overwhelmingly benign and are clinically insignificant. Simple renal cysts are asymptomatic and discovered incidentally by imaging. Symptoms are very rare, but could include pain from a cyst so large that there is a mass effect, or if the cyst becomes infected or hemorrhages. Observation, perhaps with serial imaging, is commonly all that is necessary, in order to rule out a developing cystic malignancy

or developing polycystic kidney disease. Interventions for those complications are rarely necessary. Complex cysts include features such as internal echogenicity, non-distinct or thickened walls, septations, or solid vascular components. The Bosniak classification system, commonly used to risk stratify adult cystic lesions, can also be applied to pediatric cysts to assess concern for malignancy.

#### 10.3.2.3 Question 2

**What other cystic lesions may be found in the kidney in children?**

#### 10.3.2.4 Answer 2

**Multilocular Cyst (Cystic Nephroma)**

Multlocular cyst, or multilocular cystic nephroma, is considered a benign entity, although related to Wilms tumor by classification. The entity presents in a bimodal pattern of young children before 4 years of age and adults after 30 years of age. The kidney may be quite enlarged and present as a palpable mass. It is understandable that the first concern is to rule out a more serious malignancy, such as a cystic Wilms Tumor. Ultrasonography and CT scan imaging cannot rule this entity out with certainty so the treatment for any multilocular cystic lesion is nephrectomy.

**Acquired Cystic Disease**

Acquired renal cystic disease is defined as bilateral cyst development in the setting of end-stage renal disease. The phenomenon has been observed most commonly in adults receiving long term hemodialysis, but it is common in children as well [11]. The majority of patients are asymptomatic, however bleeding into the cysts can cause pain or hematuria, complicated by associated coagulation defects commonly seen in uremia. Furthermore, there is an increased risk of malignancy in kidneys of patients undergoing long term dialysis, including renal cell carcinoma [12, 13]. Duration of dialysis is an important risk factor for developing malignancy although not the type of renal replacement therapy. Monitoring of cyst development and cyst characterization is recommended after 3 years of dialysis. Interestingly, cysts of acquired cystic disease tend to regress after renal transplantation, but the elevated risk of malignancy may persist for many years [14].

**Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

ADPKD is one of the most common CAKUT pathologies leading to adult dialysis or renal transplantation [15]. In contrast to the previously mentioned cystic diseases, it is inheritable. The vast majority of patients have a strong family history and the diagnosis is confirmed as renal cysts develop into adulthood. An estimated 95% of ADPDK patients will develop cysts by the third decade of life [16]. Likely complications include nephrolithiasis, UTIs/pyelonephritis, flank pain and hematuria. Associated medical problems include hypertension, hepatic and pancreatic cysts, and cerebral (Berry) aneurysms.

Well-described mutations include PKD1 and PKD2, which account for the overwhelming majority of ADPKD cases [17]. Mutations in the PKD1 gene, located on

chromosome 16p13, generally lead to an earlier onset of symptoms, compared to PKD2, located on 4q13–q23. However there is significant variability both. Each gene encodes a polycystin protein, which interacts with plasma transmembrane complexes to inhibit cell proliferation [18].

In addition to numerous extrarenal medical problems, there is an increased risk of renal adenomas associated with ADPKD, similar to acquired cystic disease. However, the incidence of renal cell carcinoma is not elevated above the risk of the general population [19]. Evaluation and risk assessment for malignancy is complicated by cystic hemorrhage, proteinacious debris, and the complex architecture of the cysts. Additional management strategies are focused on delaying the onset of dialysis as long as possible. This includes aggressive blood pressure management, pain control if the cyst sizes becomes symptomatic or bleed, or even surgical cyst decortication or nephrectomy.

### Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is much less common than ADPKD, about 1 in 10,000–50,000, and more commonly presents during childhood or even prenatally [20]. Prenatal sonography may identify bright, echogenic, enlarged kidneys. If there is severe bilateral disease, there is an increased chance of impaired lung development, particularly if oligohydramnios is noted [21]. Anydramnios may even be incompatible with life. Overall, about 85% of newborns surviving prenatally survive through infancy and the survival rate into the teenage years is about 70% [22]. Hypertension is the most significant associated medical problem, commonly requiring multiple medications. As the patient ages into adulthood, cysts may enlarge as seen below (Fig. 10.3) and hepatic fibrosis is an expected cormobidity related to the genetic pathophysiology.

The severity of the disease is dependent on the nature of the genetic defect. ARPKD is caused by mutations in the polycystic kidney and hepatic disease 1 gene (PKHD1), which is located on chromosome 6p21 and encodes a protein called fibrocystin [23]. Fibrocystin belongs to a class of proteins regulating cell proliferation and cellular adhesion/repulsion [24].

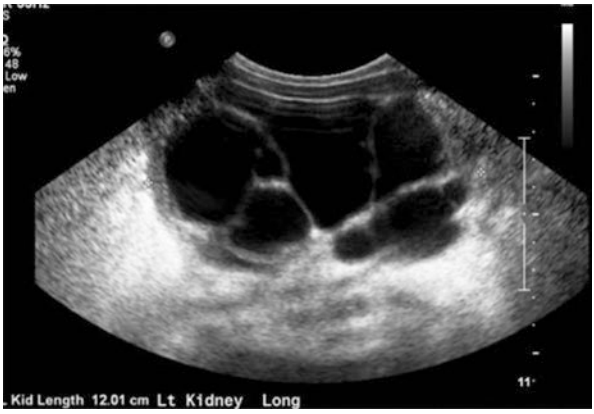


**Fig. 10.3** Renal ultrasound of the left kidney, sagittal view

It is difficult to provide a prognosis for patients with ARPKD since the clinical spectrum is so diverse. However, treatment is focused on supportive pulmonary care, particularly in infancy, management of hypertension, and renal replacement and hepatic failure, including decompression of portal hypertension.

**Syndromes with Renal Cysts**

Tuberous sclerosis and von Hippel Lindau (VHL) are two autosomal dominant disorders most commonly encountered by pediatric urologists due to the fact that cystic dysplasia is a common feature. Tuberous sclerosis complex (TSC) is a neurocutaneous disorder characterized by the classic triad of epilepsy, mental retardation and adenoma sebaceum (angiofibromas). However, there are a variety of other major and minor criteria that now help comprise a diagnosis of TSC. Renal angiomyolipomas and renal cysts are two of those possible features. *TSC1* and *TSC2* genes are located on chromosome 9q34 and 16p13 respectively. TSC1 encodes the protein hamartin and TSC2 encodes tuberin. They are both important tumor suppressor genes part of the well described mTOR pathway [25]. Renal angiomyolipomas occur in over 50% and renal cysts develop in over 20% of patients with TSC [26]. Management of TSC renal lesions is most commonly focused on preventing hemorrhage of large angiomyolipomas. In general, sizes greater than 4 cm in diameter merit consideration for prophylactic embolization or surgical excision. Annual surveillance with ultrasonography or CT scan is a reasonable approach. A small association with renal cell carcinoma is also worth noting, although likely only about 2% [27].

VHL disease is also characterized by a spectrum of renal and extrarenal manifestations. They include angiomatous renal lesions, cerebellar hemangioblastomas, pheochromocytoma, epididymal cystadenoma, clear cell carcinoma of the kidney, and cysts of the pancreas, kidney, and epididymis. It is a rare diagnosis with a high penetrance in affected patients. The *VHL* gene is a tumor suppressor gene located on chromosome 3p25. The mean age of presentation is 35–40 years of age and most frequently presents with renal cysts [28]. They are frequently multiple and bilateral cysts. Careful surveillance is the most important job of the urologist, since the risk of clear cell renal cell carcinoma is approximately 50% in VHL patients and the risk of pheochromocytoma is estimated to be over 10% [29]. The recommended mindset is not cancer cure, but cancer control, which can be a challenging balance of surgical excision of enlarging, dangerous appearing cysts, while preserving as much renal parenchyma and adrenal gland tissue as possible.

### 10.3.3 Scenario 3

**A 3 month old infant had an antenatal diagnosis of a possible multi cystic dysplastic right kidney. An ultrasound scan at 3 months is shown below** (Fig. 10.4).

#### 10.3.3.1 Question 1

**What is the differential diagnosis?**

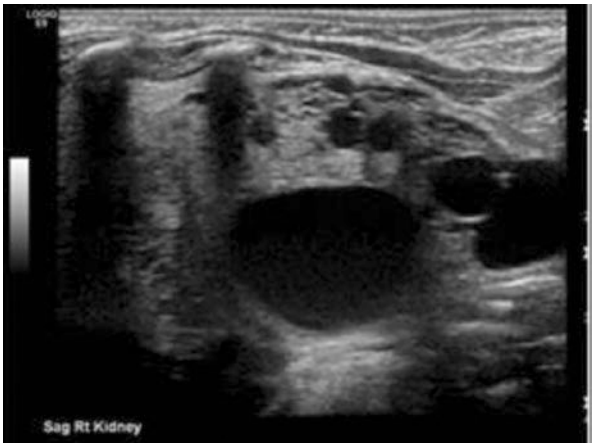


**Fig. 10.4** Renal ultrasound of the right kidney, sagittal view

#### 10.3.3.2 Answer 1
Differential diagnosis can include an MCDK, or a UPJ obstruction.

#### 10.3.3.3 Question 2
**What further imaging would you consider?**

#### 10.3.3.4 Answer 2
As a UPJ obstruction is being considered, A MAG 3 renogram should be considered.

#### 10.3.3.5 Question 3
**The MAG 3 renogram is shown below** (Fig. 10.5)**. What does this show and what would be your diagnosis?**

#### 10.3.3.6 Answer 3
The lack of function in the right kidney would be consistent with a right MCDK.

#### 10.3.3.7 Question 4
**What would be your subsequent management of the MCDK?**

#### 10.3.3.8 Answer 4
**Multicystic Dysplastic Kidney**.

##### Overview
MCDK represents the most common congenital cystic anomaly of the kidney, and is characterized by multiple non-communicating cysts with non-functional, minimal parenchyma. The size of the kidney may vary tremendously, from a small nubbin of tissue to a size capable of exerting a mass effect on other abdominal structures.


**Fig. 10.5** MAG-3 study, functional/cortical phase

Unlike other cystic kidney diseases, there is not a clear etiology for MCDK. It occurs sporadically and a variety of embryologic hypotheses have been proposed:

1. MCDK represents the most extreme form of congenital obstruction, occurring early in nephrogenesis [30]
2. Abnormalities of reciprocal induction between the ureteric bud and metanephric blastema [31]

The incidence of MCKD is about 1 in 4000 and is more common in males. Although the contralateral kidney must be "normal" for the fetus to be compatible with life, there is a higher incidence of ureteropelvic junction obstruction (about 10%) and vesicoureteral reflux (about 25%) in the contralateral kidney [32, 33] Historically, a palpable mass per abdomen was the most common presentation. Today, the overwhelming majority of MCDK is discovered during antenatal ultrasonography. The hallmark appearance is a cluster of non-communicating cysts of varying sizes. In contrast, the cystic appearance of a dilated ureteropelvic junction obstruction should be a more organized appearance of smaller cysts around a larger dilated renal pelvis, and they should communicate.

MCKD should demonstrate almost no renal parenchyma. If the diagnosis is in doubt, a nuclear scan such as DMSA or MAG3 scan should confirm an absence of any function.

### MCKD Management

A uniform management strategy for MCKD has not been established, however the recent trend has been towards less aggressive treatment regarding both imaging investigations, as well as surgery. First, if congenital hydronephrosis is present in the contralateral kidney, there is a greater concern for concurrent ureteropelvic junction obstruction. Ultrasongrapy and MAG3 scan can reliably

distinguish obstruction vs physiologic hydronephrosis. Likewise, consideration of VCUG has been advocated to assess for contralateral vesicoureteral reflux. However, as our understanding of the natural history of reflux has evolved towards a non-surgical approach, the impetus for proactively assessing for reflux has diminished as well. Furthermore, recent studies have highlighted that the majority of reflux diagnosed by VCUG is low grade and likely to resolve spontaneously [34]. In this light, VCUG imaging in the setting of a MCDK diagnosis may be considered optional.

In the past, there has also been a concern regarding malignant transformation of MCDK due to reports of both Wilms tumor and Renal Cell Carcinoma. For this reason, prophylactic nephrectomy has been considered. However, numerous studies have demonstrated that the risk of malignancy is not increased [35, 36], including data from a large MCKD registry [37]. Similarly, the risk of other surgical indications for removal, such as hypertension, remains somewhat controversial. While there have been case reports of successful hypertension resolution following MCKD nephrectomy [38], this remains uncommon.

A final consideration regarding conservative versus surgical management for MCKD is the natural history. The majority of MCKD kidneys regress and involute over time. The MCKD registry noted an undetectable ultrasound appearance of 20 by 3 and 50% by 5 years [9]. Many urologists elect to follow MCKD with serial ultrasound imaging, as it is safe to observe a progressively decreasing size in an asymptomatic patient. The frequency and duration of this monitoring is not known and a failure to regress or failure to completely involute are relative indications for surgery.

## References

1. Little MH, McMahon AP. Mammalian kidney development: principles, progress, and projections. Cold Spring Harb Perspect Biol. 2012;4:a008300.
2. Meyer R. Normal and abnormal development of the ureter in the human embryo; a mechanistic consideration. Anat Rec. 1946;96(4):355–71.
3. Whitten SM, Wilcox DT. Duplex systems. Prenat Diagn. 2001;21:952–7.
4. Bisset GS III, Strife JL. The duplex collecting system in girls with urinary tract infection: prevalence and significance. AJR Am J Roentgenol. 1987;148(3):497–500.
5. Afshar K, Papanikolaou F, Malek R, Bagli D, Pippi-Salle JL, Khoury A. Vesicoureteral reflux and complete ureteral duplication. Conservative or surgical management? J Urol. 2005;173(5):1725–7.
6. Belman AB, Filmer RB, King LR. Surgical management of duplication of the collecting system. J Urol. 1974;112(3):316–21.
7. Hensle TW, Reiley EA, Ritch C, Murphy A. The clinical utility and safety of the endoscopic treatment of vesicoureteral reflux in patients with duplex ureters. J Pediatr Urol. 2010;6(1):15–22.
8. Cain MP, Pope JC, Casale AJ, Adams MC, Keating MA, Rink RC. Natural history of refluxing distal ureteral stumps after nephrectomy and partial ureterectomy for vesicoureteral reflux. J Urol. 1998;160(3 Pt 2):1026–7.
9. De Caluwe D, Chertin B, Puri P. Fate of the retained ureteral stump after upper pole heminephrectomy in duplex kidneys. J Urol. 2002;168(2):679–80.

10. Caldamone AA, Snyder HM III, Duckett JW. Ureteroceles in children: followup of management with upper tract approach. J Urol. 1984;131(6):1130–2.
11. Hakim RM, Breyer J, Ismail N, Schulman G. Effects of dose of dialysis on morbidity and mortality. Am J Kidney Dis. 1994;23(5):661–9.
12. Resseguie LJ, Nobrega FT, Farrow GM, Timmons JW, Worobec TG. Epidemiology of renal and ureteral cancer in Rochester, Minnesota, 1950-1974, with special reference to clinical and pathologic features. Mayo Clin Proc. 1978;53(8):503–10.
13. Truong LD, Choi YJ, Shen SS, Ayala G, Amato R, Krishnan B. Renal cystic neoplasms and renal neoplasms associated with cystic renal diseases: pathogenetic and molecular links. Adv Anat Pathol. 2003;10(3):135–59. Review
14. Heinz-Peer G, Schoder M, Rand T, Mayer G, Mostbeck GH. Prevalence of acquired cystic kidney disease and tumors in native kidneys of renal transplant recipients: a prospective US study. Radiology. 1995;195(3):667–71.
15. Fick-Brosnahan GM, Tran ZV, Johnson AM, Strain JD, Gabow PA. Progression of autosomal-dominant polycystic kidney disease in children. Kidney Int. 2001;59(5):1654–62.
16. Liapis H, Winyard PJD. Cystic diseases and developmental kidney defects. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, editors. Heptinstall's pathology of the kidney, vol. 2. 6th ed. Philadephia: Lippincott Williams and Wilkins; 2007. p. 1257–306.
17. Harris PC, Rossetti S. Molecular diagnostics for autosomal dominant polycystic kidney disease. Nat Rev Nephrol. 2010;6(4):197–206.
18. Wilson PD. Polycystic kidney disease: new understanding in the pathogenesis. Int J Biochem Cell Biol. 2004;36(10):1868–73.
19. Keith DS, Torres VE, King BF, Zincki H, Farrow GM. Renal cell carcinoma in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;4(9):1661–9. Review
20. Zerres K, Rudnik-Schöneborn S, Steinkamm C, Becker J, Mücher G. Autosomal recessive polycystic kidney disease. J Mol Med (Berl). 1998;76(5):303–9. Review
21. Winyard P, Chitty LS. Dysplastic kidneys. Semin Fetal Neonatal Med. 2008;13(3):142–51.
22. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. Pediatrics. 2003;111(5 Pt 1):1072–80.
23. Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, Dornia C, Rudnik-Schoneborn S, Konrad M, Schmitt CP, Seeman T, Neuhaus TJ, Vester U, Kirfel J, Buttner R, Zerres K. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int. 2005;67(3):829–48.
24. Wang S, Zhang J, Nauli SM, Li X, Starremans PG, Luo Y, Roberts KA, Zhou J. Fibrocystin/polyductin, found in the same protein complex with polycystin-2, regulates calcium responses in kidney epithelia. Mol Cell Biol. 2007;27(8):3241–52.
25. Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, Zonnenberg B, Verhoef S, Halley D, van den Ouweland A. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype--phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. Eur J Hum Genet. 2005;13(6):731–41.
26. Chonko AM, Weiss SM, Stein JH, Ferris TF. Renal involvement in tuberous sclerosis. Am J Med. 1974;56(1):124–32.
27. Bernstein J. Renal cystic disease in the tuberous sclerosis complex. Pediatr Nephrol. 1993;7(4):490–5. Review
28. Neumann HP, Bender BU, Schultze-Seemann W, Krause T, Altehoefer C, Scheremet R, Orszagh M, Schwarzkopf G, Januszewicz A, Janetschek G, Riegler P. The kidney and von Hippel–Lindau disease: impact of molecular genetic analysis of the VHL gene for clinical management. Contrib Nephrol. 1997;122:102–8. Review
29. Levine E, Collins DL, Horton WA, Schimke RN. CT screening of the abdomen in von Hippel-Lindau disease. AJR Am J Roentgenol. 1982;139(3):505–10.
30. Tanagho EA. Surgically induced partial urinary obstruction in the fetal lamb. 3. Ureteral obstruction. Investig Urol. 1972;10(1):35–52.
31. Mackie GG, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. J Urol. 1975;114(2):274–80.

32. al-Khaldi N, Watson AR, Zuccollo J, Twining P, Rose DH. Outcome of antenatally detected cystic dysplastic kidney disease. Arch Dis Child. 1994;70(6):520–2.
33. Flack CE, Bellinger MF. The multicystic dysplastic kidney and contralateral vesicoureteral reflux: protection of the solitary kidney. J Urol. 1993;150(6):1873–4.
34. Calaway AC, Whittam B, Szymanski DM, Misseri R, Kaefer M, Rink RC, et al. Multicystic dysplastic kidney: is an initial voiding cystourethrogram necessary? Can J Urol. 2014;21:7510–4.
35. Beckwith JB. Wilms tumor and multicystic dysplastic kidney disease. Editorial Comment J Urol. 1997;158:2259–60.
36. Noe HN, Marshall JH, Edwards OP. Nodular renal blastema in the multicystic kidney. J Urol. 1989;142:486–8.
37. Aslam M, Watson AR, on behalf of the Trent & Anglia MCDK Study Group. Unilateral multicystic dysplastic kidney: long term outcomes. Arch Dis Child. 2006;91:820–3.
38. Snodgrass WT. Hypertension associated with multicystic dysplastic kidney in children. J Urol. 2000;164(2):472–3;discussion 473–4