Cystic Renal Disease

14

Katherine MacRae Dell

Core Messages

- Cystic kidney disease in neonates often presents with ultrasonography findings of diffusely echogenic kidneys with variable degrees of kidney enlargement rather than discrete cysts.
- Autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant PKD (ADPKD), and diffuse cystic dysplasia can present in the neonate with features that may be indistinguishable from each other.
- With the emergence of modern dialytic therapy, the major contributor to mortality in the neonate with severe cystic kidney disease is respiratory failure (related to oligohydramnios and pulmonary hypoplasia) rather than complications of renal failure.
- Prognosis may be difficult to predict in cystic disease in the newborn, but the presence of oligohydramnios and pulmonary hypoplasia generally is associated with poor long-term renal outcome.

Case Vignette

A male fetus was noted to have large echogenic kidneys on a prenatal ultrasound obtained at 18 weeks gestation. At 28 weeks gestation, oligohydramnios was noted as well as persistence of enlarged kidneys. The infant was born at 38 weeks gestation and developed respiratory distress in the delivery room requiring resuscitation and mechanical ventilatory support. Chest radiograph demonstrated diffuse ground glass opacities within the lungs as well as a right pneumothorax. Physical exam was notable for large palpable bilateral abdominal masses. Postnatal renal ultrasonography showed bilateral markedly echogenic kidneys measuring 7 cm (right) and 6.6 cm (left). No cysts or hydronephrosis was seen. Liver ultrasonography was normal. A chest tube was placed for management of the pneumothorax. The patient was initially oliguric, but urine output improved with initiation of furosemide. On day of life 3, he was extubated and weaned to room air by day of life 5. At 1 week of life, he developed hypertension, requiring treatment with enalapril and continuation of furosemide. He was started on enteral feeds with maternal breast milk. Because of rising serum potassium, sodium-potassium polystyrene resin was added to the feeds

K.M. Dell, MD
Division of Pediatric Nephrology,
Pediatric Kidney Transplant, UHCMC,
UH Rainbow Babies & Children's Hospital,
11100 Euclid Ave, Cleveland, OH 44106, USA
e-mail: katherine.dell@uhhospitals.org

A.S. Chishti et al. (eds.), *Kidney and Urinary Tract Diseases in the Newborn*,
DOI 10.1007/978-3-642-39988-6_14, © Springer-Verlag Berlin Heidelberg 2014

for potassium binding. He was discharged from the nursery at 3 weeks of life. Serum creatinine at that time was 0.65 mg/ dl.

14.1 Introduction

Historically, terms such as "polycystic kidneys" and "infantile polycystic kidney disease" were used to describe a variety of disorders with shared features of cysts evident either radiographically or by pathologic examination [12]. However, as our understanding of modern molecular genetics has continued to expand, it has become evident that many of these disorders have distinct genetic and pathophysiologic features. Cystic kidney disease in neonates is now recognized as representing a spectrum of disorders from those inherited in classic Mendelian fashion (such as ARPKD) to those that occur sporadically (such as multicystic dysplastic kidney, MCDK). With the advent of modern obstetrical ultrasonography, the majority of these disorders are identified prenatally. In many cases the diagnosis of a particular cystic kidney disease is suspected based on the prenatal images. However, even with advanced technology, the findings/diagnosis on prenatal ultrasonography may not be confirmed on postnatal imaging.

Many of the specific diseases addressed in detail in this chapter are uncommon. Taken as a whole, however, they represent important causes of morbidity and mortality in the newborn. It is also important to recognize that even in cases of severe neonatal renal disease, including the more severe forms of cystic kidney disease, renal supportive therapy including infant dialysis is often achievable. However, newborns with a history of severe oligohydramnios and resultant pulmonary hypoplasia may not be viable despite even the most advanced ventilatory support. Thus, the cause of mortality in these patients is usually respiratory, not renal, failure.

14.2 Background

14.2.1 Developmental Considerations

Developmentally, congenital cystic kidney diseases result from one of two general pathways. With the classic polycystic kidneys diseases (such as ARPKD and ADPKD), nephrogenesis occurs normally; then, depending on the underlying genetic disorder, cysts develop along one or more of the nephron segments. In the cystic dysplastic disorders, a defect occurs during nephrogenesis, resulting in primitive nephrons with disorganized and poorly differentiated collecting ducts [45].

14.2.2 Presentation of Cystic Kidney Diseases in the Neonate

Although the polycystic kidney diseases and cystic dysplastic disorders have distinct clinical and pathophysiologic features, they typically present in one of two ways. As the case vignette illustrates, the first presentation is that of diffusely echogenic kidneys (typically quite enlarged) evident ultrasonographically (Fig. 14.1). On physical exam, palpable abdominal masses are evident. Patients with severe bilateral disease (regardless of the underlying etiology) typically have a history of fetal oligohydramnios. This can result in the features of the oligohydramnios sequence, which include Potter's facies (Fig. 14.2), pulmonary hypoplasia, hip dislocation, extremity contractures, and club feet. The second presentation is that of one or more discrete cysts also detected ultrasonographically (Fig. 14.3). Kidneys may be enlarged or normal in size. Palpable abdominal masses are typically not evident in these cases, and a history of oligohydramnios is usually absent. In some instances (such as ADPKD) the presentation can be that of either enlarged echogenic kidneys or discrete cysts with or without kidney enlargement. Similarly, there may be instances where a few small discrete cysts are evident in enlarged echogenic kidneys (e.g., diffuse cystic dysplasia) or instances in which

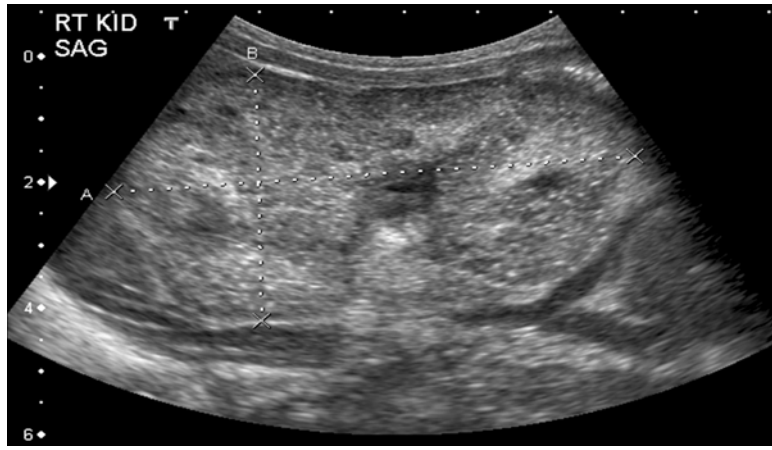

Fig. 14.1 *Enlarged echogenic kidneys*. Ultrasonography of the right kidney from a newborn with ARPKD demonstrates typical kidney enlargement as well as markedly increased echogenicity (brightness when compared to the surrounding liver parenchyma). Similar features were present on the left kidney (not shown). A few very small cysts are evident, which are often absent in neonates with this disease. This ultrasonographic appearance can also been seen in other congenital cystic kidney disease including ADPKD, diffuse cystic dysplasia, and infantile nephronophthisis (Courtesy of Dr. Rashini Parikh, Department of Radiology, University Hospitals Case Medical Center, Cleveland, Ohio)

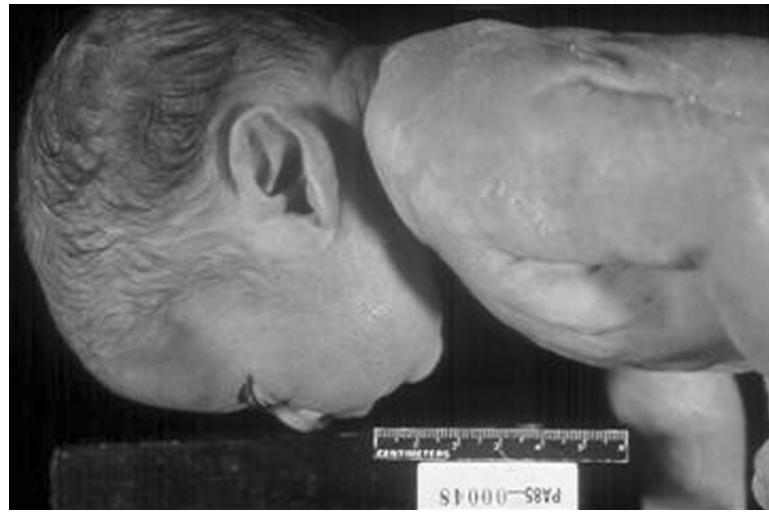

Fig. 14.2 *Potter's facies*. The photograph obtained at autopsy shows a fetus with Potter's facies, a feature of the oligohydramnios sequence. Additional features of the sequence include pulmonary hypoplasia, hip dislocation, and club foot (Courtesy of Dr. Gretta Jacobs, Department of Pathology, University Hospitals Case Medical Center, Cleveland, Ohio)

kidneys are echogenic, but are typically not enlarged (e.g., infantile nephronophthisis).

14.2.3 Differential Diagnosis of Cystic Kidney Diseases

Cystic kidney disorders that present in neonates are outlined in Table 14.1. The typical presentation (enlarged echogenic kidneys, discrete cysts, or either) is indicated by the key below. However, presentations can be variable and considerable overlap can occur, which may make it difficult to determine definitive diagnosis in the newborn period [20]. In one published series, of 93 fetuses with echogenic kidneys (and confirmed nephropathy postnatally), approximately 30 % had visible cysts [9]. In that same series, 33 % of the subjects had ARPKD, 30 % had ADPKD, 12 % had Bardet-Biedl syndrome, 10 % had

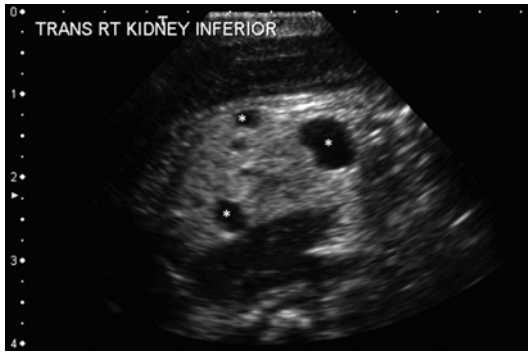

Fig. 14.3 *Renal macrocysts*. Renal ultrasonography of the right kidney from a neonate with ADPKD demonstrates several macroscopic cysts (indicated with *asterisk*). The left kidney demonstrated 2 small cysts (not shown). The kidneys also show mildly increased echogenicity and mild enlargement bilaterally

Meckel-Gruber syndrome, and the remaining 15 % had a variety of other cystic kidney diseases [9]. It should also be noted that congenital obstructive uropathies may sometimes present on prenatal ultrasonography as "cystic kidneys" due to marked dilatation of the collecting systems. On postnatal evaluation, however, the diagnosis of obstructive uropathy is usually evident (see Chaps. 8, 10, and 11).

14.3 Polycystic Kidney Diseases

Genetics, clinical features, diagnosis, treatment, and prognosis for the inherited polycystic kidney diseases that present in neonates, including ARPKD, ADPKD, glomerulocystic kidney disease, and juvenile nephronophthisis, are discussed below.

14.3.1 Autosomal Recessive Polycystic Kidney Disease (ARPKD)

14.3.1.1 Genetics, Clinical Features, and Diagnosis

ARPKD is a relatively rare disorder, affecting 1:40,000 patients. As the name suggests, it is inherited as an autosomal recessive trait [13].

Table 14.1 Cystic kidney diseases that present in the neonate

Polycystic kidney diseases	Autosomal recessive polycystic kidney disease (ARPKD)[a]
–	Autosomal dominant polycystic kidney disease (ADPKD)[b]
–	ADPKD associated with tuberous sclerosis[c]
–	Glomerulocystic kidney disease[b]
	Juvenile nephronophthisis[a]
Cystic dysplasia	Diffuse cystic dysplasia[a]
	Isolated/sporadic
	Associated with congenital syndromes (e.g., Meckel-Gruber, Bardet-Biedl, Jeune, Beckwith-Wiedemann)
–	Multicystic dysplastic kidney[c]
Other causes of renal cysts in neonates	Simple renal cysts[c]
	Caliceal diverticulum[c]

[a]Typically present with diffusely echogenic kidneys with varying degrees of enlargement
[b]Present with either echogenic kidneys, discrete cysts, or both
[c]Typically present with discrete cysts

Males and females are equally affected and all races are affected as well. ARPKD is caused by mutations in the *polycystic kidney and hepatic disease* (*pkhd1*) gene [44]. This gene encodes a very large protein, fibrocystin/polyductin. Mutations are present throughout the gene, with most families having "private" mutations not shared by other kindreds. Genotype-phenotype correlations have not been well established, although it has been proposed that patients with severe mutations that result in little or no protein production may have a very high rate of neonatal mortality [3]. Although the genetics of the disease have been identified, the mechanisms by which the abnormal protein induces pathology remain undefined. Emerging data suggest that alterations in intracellular signaling and mechanosensation mediated through a cellular organelle called the primary cilia are thought to play a major role in the pathophysiology of these diseases [21].

ARPKD primarily affects only the kidneys and liver [13]. The polycystic kidney disease is characterized by microscopic fusiform dilatations affecting all of the collecting tubules (Fig. 14.4).

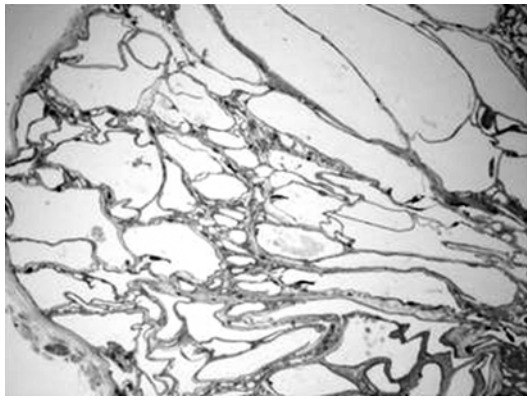

Fig. 14.4 *ARPKD kidney pathology*. Histologic findings in ARPKD kidney disease are shown, including radially oriented, diffuse fusiform dilatations of the collecting tubules (Courtesy Dr. Gretta Jacobs, Department of Pathology, University Hospitals Case Medical Center, Cleveland, Ohio)

These "microcysts" give the radiographic appearance of very enlarged and markedly echogenic kidneys. A few discrete cysts may still be evident in some patients, but this is less common. The liver disease in ARPKD (congenital hepatic fibrosis, CHF, also called Caroli's disease) is a biliary abnormality characterized by proliferation and cystic changes in the bile ducts with accompanying periportal fibrosis [39]. Discrete liver cysts are typically absent. In neonates, the kidney disease predominates, and radiographic or laboratory evidence of hepatic involvement (e.g., echogenic liver) is present in only 40 % [47]. The other signs and symptoms associated with ARPKD, including pulmonary hypoplasia and Potter's facies, are the sequelae of the oligohydramnios sequence rather than a direct result of the mutated gene.

The case vignette highlights the typical presentation of ARPKD in the neonate. Affected infants, particularly those with a history of oligohydramnios, commonly develop respiratory distress in the delivery room and require mechanical ventilation. Respiratory compromise develops not only because of pulmonary hypoplasia but also because the massively enlarged kidneys may prevent adequate diaphragmatic excursion. Renal complications seen in the newborn period include oliguria and elevated serum creatinine (both of which may improve in the short term), hyponatremia, and hypertension [14].

The diagnosis of ARPKD is usually made based on clinical criteria [19, 47]. These include the presence of enlarged echogenic kidneys, absence of cysts in the parents, and one or more of the following: ultrasonographic or histologic evidence of liver disease, parental consanguinity, and/or biopsy proven ARPKD in a sibling/previous pregnancy. Renal imaging of the parents is important in ruling out the possibility of ADPKD, although ADPKD cannot be definitively ruled out unless the parents are older than 30 years of age. Renal or liver biopsies are generally not undertaken for diagnosis purposes, but may be indicated in some patients in whom the diagnosis is unclear.

Genetic testing is generally not necessary in the immediate newborn period because treatment is the same regardless of the underlying cause of the kidney disease. Confirmation of the diagnosis is, however, important for counseling of future pregnancies as well as defining risk (if any) to existing siblings. Thus, families of a child with suspected ARPKD should be referred for genetic counseling. Molecular genetic testing in the form of direct gene sequencing is available for ARPKD and has an accuracy of about 85 % in detecting mutations [3, 38]. For an updated listing of laboratories performing clinical genetic testing for ARPKD and other inherited diseases, see www.geneclinics.org. If a fetus or neonate with suspected cystic kidney disease expires, autopsy should be encouraged in order to definitely establish the diagnosis for counseling of future pregnancies. Consultation with a geneticist should be undertaken in the immediate newborn period if the infant has evidence of syndromic features or extrarenal manifestations other than hepatic disease, as those patients may have diffuse cystic dysplasia associated with a congenital syndrome rather than ARPKD.

14.3.1.2 Treatment and Prognosis

There are currently no disease-specific therapies available in clinical practice. Treatment

of ARPKD in the newborn period is primarily focused on respiratory support, fluid and electrolyte balance, and control of hypertension. Consultation with a pediatric nephrologist is essential for the management of these issues. The hypertension can be severe and can occur within the first week of life. Angiotensin converting enzyme inhibitors (ACEI) are considered the treatment of choice, but have not been systematically studied in patients. In addition, acute kidney injury in the newborn period may limit their use in the initial treatment of hypertension in the newborn. Markedly enlarged kidneys contribute to significant feeding intolerance, and achieving adequate nutrition can be very challenging in this population. Based on case reports, some have advocated performing unilateral nephrectomy to relieve both respiratory and feeding difficulties [2]; however, this has not been systematically studied. Rapid growth of the contralateral kidney may eliminate any brief benefit derived from the procedure (unpublished observation).

ARPKD was once considered a uniformly fatal disease for affected infants. With modern neonatal support, this is clearly no longer the case. Nevertheless, mortality in the newborn period is still significant: approximately 30 % of affected infants will die in early infancy, typically from respiratory failure [4]. The long-term complications for infants that survive the newborn period include chronic lung disease, chronic kidney disease (CKD), growth failure, and hepatic complications (varices, portal hypertension, ascending cholangitis) [19]. Approximately 50 % of patients will progress to ESRD within the first decade of life. Based on data generated from the 1950s to the 1990s, 10-year patient survival is 80 % [33]. However, longer-term morbidity and mortality, particularly as it relates to complications of the hepatic disease, are less well defined. The lack of data is due to a number of factors including the more slowly progressive nature of CHF and the fact that many of the children who now survive and undergo kidney transplantation have not yet reached adulthood. Thus, it is likely that complications related to liver disease will become a greater contributor to morbidity and mortality as this population ages.

14.3.2 Autosomal Dominant Polycystic Kidney Disease (ADPKD)

14.3.2.1 Genetics, Clinical Features, and Diagnosis

ADPKD is the most common inherited kidney disease, with a prevalence of 1:1,000 persons [42]. Historically, it was considered a disorder of adulthood; in fact, it has been alternatively named "adult polycystic kidney disease," presumably to distinguish it from ARPKD. While the majority of patients do present in adulthood, it is clear that the disease may present in children, infants, and, rarely, fetuses [10, 41]. ADPKD is inherited as an autosomal dominant trait and is caused by mutations in one of two genes, *PKD1* (85 % of patients) or *PKD2* (15 % of patients) [23]. Consistent with the autosomal dominant inheritance, all patients will develop renal cysts over time. However, there is considerable variation in the disease expression both between families and within members of the same family. Thus, parents of a child with ADPKD may be asymptomatic and unaware that they are affected. In addition, in about 10–15 % of cases, there is no family history of ADPKD and such patients have a new mutation. Because the genes for tuberous sclerosis (*TSC2*) and ADPKD (*PKD1*) lie adjacent to each other on chromosome 16, ADPKD can also be inherited as part of a contiguous gene syndrome [31].

ADPKD is a systemic disease affecting multiple organs. In addition to polycystic kidneys, affected patients can have liver and pancreatic cysts as well as vascular abnormalities, including cerebral and aortic aneurysms and mitral valve prolapse. Young children, however, generally do not show the extrarenal manifestations of ADPKD, and the clinical signs and symptoms of ADPKD can be highly variable. Older children and adults with ADPKD typically present with symptoms such as gross hematuria or elevated blood pressures or are diagnosed after incidental identification of renal cysts while undergoing abdominal imaging for a nonrenal indication. In contrast, newborns with ADPKD are usually identified based on prenatal ultrasonographic

findings of one or more discrete cysts (78 % in one series) or with diffusely echogenic kidneys that may be indistinguishable from ARPKD [20, 37]. Clinical signs and symptoms of ADPKD in newborns can be variable [10]. Infants with macrocysts are usually asymptomatic or may have hypertension or urinary tract infection. Infants with diffusely enlarged echogenic kidneys may have clinical features that mirror those of ARPKD, including oliguric acute kidney injury with electrolyte abnormalities, respiratory distress, hypertension, and large palpable abdominal masses on physical exam. Infants with ADPKD as a manifestation of the *PKD1*/*TSC2* contiguous gene syndrome tend to have a severe presentation and may be misdiagnosed as having severe early onset ADPKD alone or ARPKD [34, 40].

Diagnosis of ADPKD in the newborn is generally based on family history and clinical features. The presence of cysts or enlarged echogenic kidneys in a neonate or infant with a parent with ADPKD is considered diagnostic [23]. As noted above, abdominal imaging should be considered in parents of infants with renal cysts or diffuse echogenicity in order to distinguish ADPKD from ARPKD or isolated diffuse cystic dysplasia. However, it should be noted that ADPKD cannot be definitively excluded in parents who are under the age of 40. Because the incidence of simple cysts in children is very low, the presence of several cysts on each kidney is highly suggestive of ADPKD, even in the absence of a positive family history [23]. Genetic testing is available for ADPKD, but is generally not necessary in patients with the classic features of bilateral macroscopic renal cysts. It may be helpful in patients with diffusely echogenic kidneys for whom alternative diagnoses (notably diffuse cystic dysplasia or ARPKD) are not clearly evident. As with ARPKD, parents of newborns with suspected ADPKD should be referred for genetic counseling in order to understand and define the risk for future pregnancies as well as for existing siblings.

14.3.2.2 Treatment and Prognosis

As is the case for ARPKD, there are no disease-specific therapies for ADPKD, although clinical trials in adults with ADPKD are under way [8]. Treatment at all ages is primarily supportive and directed at the specific symptoms (if present). Patients with macroscopic cysts who are otherwise asymptomatic should be monitored for the development of hypertension. Urinary tract infection or gross hematuria may develop rarely in young children. Infants with severe disease should be treated similarly to severely affected ARPKD neonates as outlined above.

Prognosis for patients with very early onset ADPKD (<18 months at presentation) depends, in large part, on the nature of their initial presentation (asymptomatic with macrocysts versus severe symptomatology with enlarged echogenic kidneys). Although it was initially thought that the majority of infants with early onset disease would have a poor prognosis, a recent study suggests that over 90 % of the infants initially identified by screening ultrasonography maintained normal to near-normal kidney function well into childhood [37]. In contrast, infants with ADPKD as part of the *TSC2*/*PKD1* complex generally have a poorer renal prognosis [34]. Importantly, patients with the *TSC2*/*PKD1* complex are also at risk for development of other TS-related complications, such as central nervous system lesions, renal angiomyolipomata, and renal cell carcinoma [40].

14.3.3 Other Inherited Cystic Kidney Diseases

14.3.3.1 Juvenile Nephronophthisis

Juvenile nephronophthisis (JN) is an autosomal recessive disorder characterized by chronic tubulointerstitial nephritis [46]. Although rare, it accounts for up to 10 % of pediatric end-stage renal disease (ESRD). The majority of patients with JN present in childhood and progress to ESRD in later childhood or adolescence. However, approximately 10 % have an "infantile" presentation, with most presenting in the first year of life [43]. Infantile forms of JN are caused by mutations in one of two genes, *nphp2* and *nphp3*, which are part of a large family of genes that encode proteins

called nephrocystins [46]. However, a significant proportion (up to 50 %) of patients with infantile JN will not have an identifiable mutation in any of the nephronophthisis genes.

The clinical signs and symptoms of the infantile form are variable. Kidneys may be enlarged, normal sized, or small, but all demonstrate increased echogenicity [25, 43]. Small cysts are present histologically (usually in the corticomedullary region) but are often not visualized by ultrasonography. Common symptoms at presentation include anemia, polyuria, and failure to thrive. Unlike the childhood and adolescent forms, hypertension is a predominant finding in the infantile form. In addition, extrarenal manifestations are common, including cardiac valvular and hepatic disease. Notably congenital hepatic fibrosis (CHF), which is also present in ARPKD, is reported to be evident in 40 % of patients with the infantile form [43].

Diagnosis is based on typical histologic findings on kidney biopsy. Although the presence of CHF may suggest the diagnosis of ARPKD, the majority of patients with infantile JN do not have enlarged kidneys. On the other hand, if the kidneys are small or normal sized, it may be difficult to distinguish infantile JN from cystic dysplasia, particularly the hypoplastic form of glomerulocystic kidney disease.

Treatment is directed at managing the complications of chronic kidney disease (CKD). Unfortunately, rapid progression to ESRD by age 3 years occurs in the vast majority of patients with the infantile JN [43].

14.3.3.2 Glomerulocystic Kidney Disease

Glomerulocystic kidney disease (GCKD) is a descriptive term that was historically based on the histologic appearance cysts in the Bowman's capsule [5]. It is now recognized that this finding may be a manifestation of any number of cystic kidney diseases [7]. These include the polycystic kidney diseases as well as cystic dysplastic disorders associated with congenital malformation syndromes. Specific disorders that are classically associated with glomerular cysts include ADPKD in very young infants and ADPKD that occurs in association with tuberous sclerosis. Glomerular cysts are also a prominent feature of the "hypoplastic" form of glomerulocystic kidney disease, an heritable form of cystic dysplasia that is now known to be caused by inherited mutations in the *hepatocyte nuclear factor-1 beta* (*HNF-1β*) gene. Although less common, glomerular cysts may also be found in certain forms of JN as well as in cases of severe obstructive uropathy that result in dysplasia [7].

14.4 Cystic Kidney Disease Associated with Dysplasia

Cystic dysplasia results from abnormal nephron development and is evident histologically by poorly formed glomeruli, primitive, disorganized tubules and cysts that may be present at any point along the nephron [45]. Cystic dysplasia encompasses a broad range of kidney disorders with variable etiologies, clinical presentations, and prognoses. Cystic dysplasia may be a manifestation of a primary sporadic or inherited congenital kidney disease or may result from secondary insults during prenatal development (such as obstructive uropathy). Cystic dysplasia may be focal (involving only part of the kidney) or diffuse, unilateral or bilateral. The primary focus of this section will be diffuse cystic dysplasia and unilateral multicystic dysplastic kidney (MCDK).

14.4.1 Diffuse Cystic Dysplasia

Diffuse cystic dysplasia typically presents on prenatal ultrasonography as bilateral echogenic kidneys without discrete cysts. Depending on the underlying etiology, kidneys may be small, normal, or enlarged in size. Diffuse cystic dysplasia occurs as a sporadic or inherited disorder or as a component of a well-defined congenital malformation syndrome.

14.4.1.1 Isolated or Familial Diffuse Cystic Dysplasia

The incidence of diffuse cystic dysplasia (not in association with a known congenital syndrome)

is not known. In one small case series of seven neonates and two fetuses without syndromic features who were diagnosed with enlarged echogenic kidneys in utero, one had histologic confirmation of diffuse cystic dysplasia [20]. It should be noted, however, that histologic confirmation of the diagnosis underlying diffusely echogenic kidneys is often not available so the true incidence is difficult to estimate.

Historically, many cases of isolated diffuse cystic dysplasia were considered sporadic, i.e., not associated with a known mutation in the patient and without a clear family history of cystic kidney disease. However, recent data has suggested that mutations in the *HNF-1B*/*TCF2* gene may underlie many cases of both sporadic and familial diffuse cystic dysplasia, including those that present prenatally with diffusely echogenic kidneys [15, 24]. The *HNF-1β* (*TCF2*) gene is located on chromosome 17 and encodes a transcription factor that is broadly expressed in the kidney, liver, pancreas, and genitalia during fetal development [11]. As noted above, it was originally recognized as the cause of familial "hypoplastic" GCKD [6]. This rare autosomal dominant disease is characterized by small echogenic kidneys on ultrasonography and histologic evidence of glomerular cysts. Mutations in HNF-1β also underlie the endocrine disorder, maturity-onset diabetes of the young (MODY), which may be associated with renal cysts. It is now recognized that the phenotype of patients who harbor mutations in HNF-1β is extremely variable, and a family history is often absent [15]. Renal manifestations, however, are the most common feature. Renal cystic kidney disease was present in 57 % of a cohort of 160 patients with HNF-1β mutations [15]. In another series, a prenatal phenotype of hyperechogenic kidneys with normal or moderately enlarged size was found in 34/56 patients with known HNF-1β mutations for whom a prenatal ultrasound was available [24]. Finally, in a series of 62 pregnancies characterized by echogenic fetal kidneys with variable degrees of enlargement, HNF-1β mutations were found in 29 %. These studies suggest that HNF-1β mutations may be a more common cause of isolated diffuse cystic dysplasia than was previously thought.

Because of the variable presentation and disease course of isolated or familial cases of diffuse cystic dysplasia, prognosis is difficult to determine. As with other renal cystic kidney diseases, such as ARPKD and ADPKD, the presence of oligohydramnios and respiratory failure in the newborn is likely to be associated with a poor renal prognosis.

14.4.1.2 Diffuse Cystic Dysplasia Associated with Congenital Malformation Syndromes

Consistent with its developmental origins, diffuse cystic dysplasia is a component of many congenital malformation syndromes. Notable examples include the syndromes of Meckel-Gruber [1], Joubert [32], and Bardet-Biedl [17] and overgrowth syndromes such as Beckwith-Wiedemann [30] and Simpson-Golabi-Behmel [18]. A complete discussion of these and other syndromes associated with cystic dysplasia is beyond the scope of this chapter. For up-to-date detailed genetic and clinical information about syndromes associated with cystic dysplasia (or "polycystic kidneys"), the reader is directed to the NIH-sponsored Online Mendelian Inheritance in Man (OMIM) website, www.ncbi.nlm.nih.gov/omim.

14.4.2 Multicystic Dysplastic Kidney (MCDK)

MCDK is a relatively common entity, occurring in 1:4,300 births, with a slight male gender and left-sided predominance [28, 35]. Most cases are sporadic, although rare familial cases of MCDK have been reported [36]. The genetic basis for the disease is not known, although MCDK has been reported in patients with mutations in one of several developmental genes including EYA1, SIX1, PAX2, and HNF-1β [11, 22].

MCDK is the most severe form of cystic dysplasia, resulting in complete disconnection between the nephron and the collecting system with no functional renal parenchyma [22]. Unlike many of the cystic kidney diseases already discussed, which may present as cysts

or diffusely echogenic kidneys, MCDK invariably presents as numerous large cysts present on one kidney. Because MCDK kidneys are nonfunctional, bilateral disease is generally not consistent with viability after birth [35]. Abnormalities in the contralateral kidney and/or the genitourinary tract are common, occurring in 36 % of patients who are diagnosed prenatally [35]. The most common of these abnormalities is vesicoureteral reflux (VUR), which occurs in 20 % of patients. Of those, 60 % have grade I or II (mild) VUR and 40 % have grade III–V (moderate–severe) VUR [35]. Other associated abnormalities include ureteropelvic junction (UPJ) obstruction, ureterovesical junction (UVJ) obstruction, or a variety of genital abnormalities such as Gartner's cysts, seminal cysts, or vaginal malformations [22].

Diagnosis is made based on the typical ultrasonographic appearance. MCDK is distinguished from ADPKD (which can present with unilateral disease) by the numerous large cysts with no apparent normal parenchyma and a contralateral kidney that is generally without cysts, enlargement, or echogenicity. In cases where there is a question of whether functioning parenchyma is present in the MCDK kidney, a radionuclide scan may be helpful [22].

The natural history of most MCDKs is involution over time, with 60 % involution by age 5 [28]. Therefore, surgical resection is generally not required, and medical management involves serial ultrasonography to confirm involution of the affected kidney and appropriate compensatory hypertrophy of the contralateral kidney as well as blood pressure, serum creatinine, and urine protein measurements [22]. In the past, nephrectomy was advocated because of rare reports of hypertension or malignancy. More recent data, however, suggest that there is no increased risk of these complications for patients with MCDK compared to the normal population [22]. Nephrectomy, therefore, is reserved for cases in which involution does not occur over time and/or the MCDK demonstrates rapid growth or the presence of a discrete mass.

Because MCDKs are nonfunctional, prognosis is determined by the status of the contralateral kidney. Those with normal-appearing contralateral kidneys that show appropriate compensatory hypertrophy generally do quite well although an increased risk of proteinuria has been reported [28]. Although long-term data are somewhat limited, those with demonstrated abnormalities in the contralateral kidney appear to have an increased risk of chronic kidney disease and hypertension [22, 28].

14.4.3 Other Causes of Renal Cysts in Neonates

Simple renal cysts occur rarely in childhood, with a reported incidence of 0.2 % [29]. Because of this rare occurrence, it is important to have a high index of suspicion for other cystic kidney disorders. Notably, ADPKD in infants and children can present as an isolated renal cyst in one kidney. In addition, in a patient with a family history of ADPKD, the finding of even one cyst in childhood may be considered diagnostic [14]. Thus, a detailed family history and serial renal ultrasonography to monitor for the development of additional ipsilateral and contralateral cysts are imperative in the evaluation of a neonate found to have a renal cyst.

Another rare cause of a solitary or "simple" renal cyst is a caliceal diverticulum. This disorder is typically unilateral and solitary and may mimic the appearance of a cyst [16, 27]. In instances where ADPKD or suspected isolated renal cyst are suspected, these can be distinguished from caliceal diverticulum either with magnetic resonance urography or computed tomography with delayed images [27]. In one series, 9 % of affected patients have contralateral VUR [16]. Complications of caliceal diverticulum include urinary tract infection and urolithiasis [26]. Management of confirmed caliceal diverticulum is generally guided by pediatric urologists. Various surgical approaches (including percutaneous ablation or marsupialization) have been undertaken in symptomatic patients, whereas asymptomatic patients are generally observed without intervention [16].

Conclusion

Renal cystic diseases in the fetus and newborn encompass a large number of disorders, some of which may be associated with life-threatening complications. It is important to recognize that the presentation of cystic kidney disease in the fetus or newborn may be that of diffusely echogenic kidneys of variable size rather than the discrete cysts typically evident in older children or adults with cystic kidney diseases. The treatment of newborns with severe suspected cystic kidney disease (regardless of the cause) is directed at respiratory support, maintenance of fluid and electrolyte balance, and treatment of hypertension. The diagnostic criteria and long-term prognosis for this heterogeneous group of disorders is variable and depends, in large part, on the nature of the underlying disorder. In general, however, a history of oligohydramnios and the development of respiratory distress from pulmonary hypoplasia suggest a poor long-term renal prognosis.

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