

CURRENT TOPIC

Imaging in cystic renal disease

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The term “cystic kidneys” is used to describe a heterogeneous group of conditions characterised either by single/multiple cysts or abnormal kidneys with no obvious cysts as the kidney may appear hyperechoic (solid). Confusion has arisen because the terminology is imprecise at times and multiple cysts do not necessarily denote a heritable condition or specific syndrome. The disorders span all ages in childhood and since the introduction of routine antenatal ultrasound many are identified antenatally.

The ultimate diagnosis of many of the “cystic kidneys” requires clinical, genetic, radiological, and pathological information. Errors arise when insufficient information is gathered and collated. A precise diagnosis is important for prognosis, treatment, and genetic counselling although this may not be possible at presentation.^{1–3} As the aetiology, histology, and clinical presentation are diverse, no single classification of “cystic renal disease” is satisfactory; the most widely acceptable classification is genetic and non-genetic (see table 1). A morphological classification of “cystic kidneys” however remains useful for the non-genetic disorders. Classification of a particular child’s “cystic kidneys” requires information about any relevant family history;

parental consanguinity; relevant histopathology if available, and ultrasound of parents and siblings. Full clinical evaluation, evidence of a syndrome or dysmorphic features, assessment of renal function, and any antenatal ultrasound findings are all important. Extrarenal manifestations occur and ultrasound examination of liver, pancreas, and spleen is mandatory.

Ultrasound

Ultrasound is the cornerstone of imaging and sequential examinations have described the natural history of many of these disorders (see table 2). At times ultrasound alone is sufficient for diagnosis, for example, multicystic kidney; however, other conditions require integration of many imaging modalities when certain conditions are being considered.

Ultrasound will identify whether the abnormality is unilateral or bilateral; symmetrical or asymmetrical; the size of the kidneys; and the presence or absence of dilatation of the collecting system. The exact location within the kidney, size, and number of cysts must be noted; the echogenicity of the cortex must be compared both to the medulla as well as to the liver/spleen. As ultrasound equipment improves, anatomic detail of the renal cortex has become better and it is now possible to detect

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Table 1 Classification of cystic renal disease

Genetic			Non-genetic
Autosomal recessive	Autosomal dominant	Cysts associated with syndromes	
Autosomal recessive polycystic kidney disease (ARPKD)	Autosomal dominant polycystic kidney disease (ADPKD)	Autosomal recessive syndromes	Cystic dysplasia or dysplasia
Juvenile nephronophthisis (JN)	Tuberous sclerosis (TS)	X linked syndromes	Multicystic dysplastic kidney
	Medullary cystic disease (MC)	Chromosomal disorders	Medullary sponge kidney
	Glomerulocystic disease		Localised cystic disease of the kidney
			Simple cysts
			Calyceal cyst
			Multilocular cyst/multilocular cystic
			Wilms' tumour
			Acquired cystic kidney disease (in chronic renal failure)

Table 2 Natural history of cystic renal disease

Predominantly cystic	Kidney size	Predominantly hyperechoic	Kidney size	Mixed/variable	Kidney size
Multicystic dysplastic kidney	Variable	Cystic dysplastic	Small	Multicystic Wilms' tumour	Large
Simple cyst	Normal	ARPKD*	Large, >90th centile	Tuberous sclerosis	Variable
Localised cystic disease	Normal	Laurence–Moon–Biedl	Normal		
ADPKD**	Large or normal	Glomerulocystic disease	Normal		
Multilocular cyst	Large				
Acquired cystic disease in chronic renal failure	Small				

*May change in later childhood to become mainly “cystic”.

**Except in prenatal.

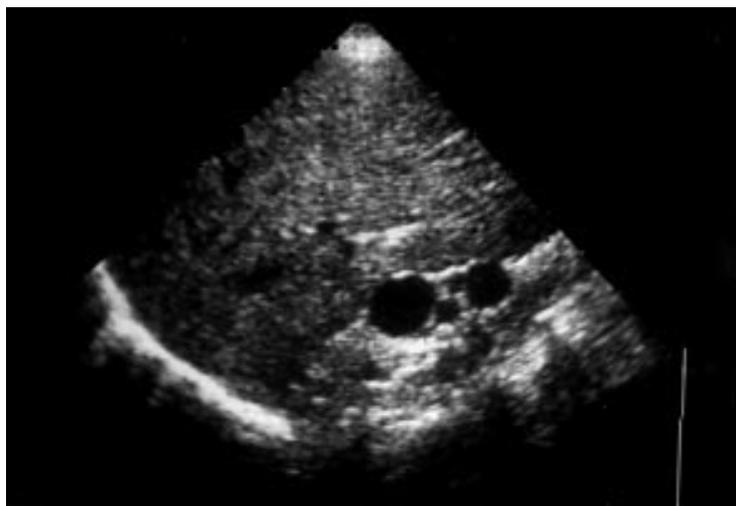


Figure 1 Cystic dysplastic kidney. Longitudinal ultrasound scan on a male neonate. The right kidney is small hyperechoic with loss of the normal corticomedullary differentiation and contains multiple small cysts. The left kidney had similar appearance. The bladder was thickwalled and the infant had posterior urethral valves.



Figure 2 Cystic dysplastic kidneys. Micturating cystourethrogram on an infant with dysplastic kidneys on ultrasound showing vesicoureteric reflux into tortuous ureters and abnormal calyces with parenchymal filling and blush.

1–2 mm transonic lesions which are probably tiny cysts. Ultrasound is expected to reach a specific diagnosis yet renal ultrasound cannot distinguish between certain conditions, for example, autosomal dominant polycystic kidney disease (ADPKD) and tuberose sclerosis in the young child. Furthermore, other imaging is usually required to look for associated abnormalities, for example, cystic dysplasia and vesicoureteric reflux; involvement of other systems, for example, the liver in Caroli's disease and autosomal recessive polycystic kidney disease (ARPKD).

Non-genetic "cystic kidney"

The nomenclature is confusing; "cysts" may be found yet cysts may simply be part of another condition, however they must be included in the differential diagnosis of "cystic disease of the kidney".

DYSPLASIA/CYSTIC DYSPLASIA

Renal dysplasia is an aberration of metanephrotic development in which the structure of the kidney is altered and glomerular as well as ductal differentiation are perturbed. There is persistence of "fetal" kidney tissue in the form of nests of metaplastic cartilage associated with primitive ducts. Pathologically, renal cystic disease and renal dysplasia are two distinct entities. This is true even though dysplastic kidneys often are cystic and many types of cystic kidneys show some dysplasia. However, the term is used without histological confirmation by the clinician. The condition may be unilateral or bilateral; when bilateral the child will go into renal failure early in life but end stage renal failure is variable and may not come about till later in life. All dysplastic kidneys function albeit poorly.⁵

Imaging

Renal ultrasound appearance includes a small kidney (less than third centile for age) with a bright echonephrogram and loss of corticomedullary differentiation. Cysts are variable both in size and number but are usually less than 1 cm. Occasionally the ultrasound appearance is dominated by these small cysts, typically subcortical in position even though the kidney remains small (fig 1). Dilatation is rarely seen on ultrasound unless associated with obstruction as in posterior urethral valves (PUV) or grade 4–5 vesicoureteric reflux (VUR).

Radiological contrast study—There is an increased incidence of VUR. When the calyces are outlined by contrast on either micturating cystogram (MCU) (fig 2) or intravenous urography (IVU) they are few in number, and show loss of the fornices with blunting; with reflux the renal pelvis may be dilated and rather perpendicular and the ureter is tortuous and dilated.

Radioisotope—The technetium-99m DMSA scan shows reduced function if unilateral, or poor visualisation of the kidneys if bilateral. The normal cool pyramids are not seen and frequently there are focal defects in the kidney which cannot be distinguished from a scar secondary to urinary tract infection (UTI). These focal defects are seen in children with dysplasia who have never had a UTI.

Dysplasia may be seen in association with malformations of the kidney, for example, the upper moiety of a duplex (fig 3), posterior urethral valves, crossed fused renal ectopia, horseshoe kidney, or the pelvic kidney. In many syndromes and genetic disorders the kidneys are affected with or without cysts; these include Beckwith–Weideman syndrome, Laurence–Moon–Beidel syndrome, Opitz–Lemi syndrome, oto-brachial-digital syndrome, Meckel's syndrome, and Zellweger's syndrome among others.⁵

MULTICYSTIC KIDNEY (MULTICYSTIC DYSPLASTIC KIDNEY)

Multicystic kidney or multicystic dysplastic kidney (MDK) causes confusion with the dysplastic/cystic dysplastic kidney as described

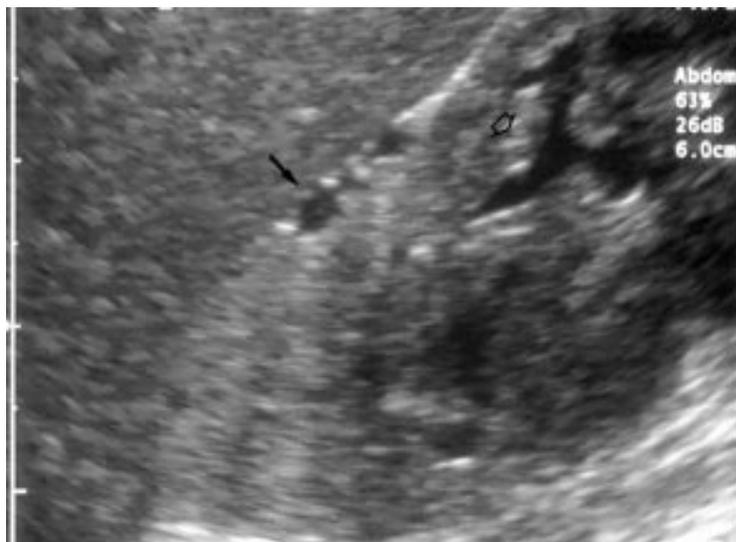


Figure 3 Dysplastic upper moiety of a duplex kidney. Longitudinal ultrasound scan of the right kidney. There are small subcortical cysts in the upper pole (arrow). The collecting system of the lower pole can be seen below (open arrow).



Figure 4 Multicystic kidney. Longitudinal ultrasound scan of the right multicystic kidney showing the classical appearance of multiple cysts of varying sizes with very little surrounding parenchyma, occupying the whole of the right kidney.

above. In MDK there is loss of lobular organisation, although small islands of renal tissue may be identified. Primitive cartilage and ductules are present, suggesting aberration of renal differentiation, the hallmark of dysplasia. Some consider MDK and cystic dysplasia as ends of the same spectrum; however, all MDK are non-functioning and have an atretic ureter. There are conflicting reports as to the incidence of VUR.

Antenatal ultrasound is the commonest presentation. MDK is commoner in males and has a natural history of involution. There are a few case reports of either hypertension or malignancy but this association is not universally accepted. The important associated abnormalities (30%) include pelvi-ureteric junction obstruction (PUJ), ureteric stenosis of the opposite kidney, and VUR.

Imaging

Ultrasound appearances vary from a small single cyst to multiple cysts of varying sizes with a

large dominant cyst situated peripherally with no identifiable renal parenchyma (fig 4). Sequential ultrasound shows that most MDK involute, some during intrauterine life. A few MDK enlarge progressively, generally in those greater than 5–6 cm at birth. Occasionally ultrasound may not distinguish between MDK and PUJ. In such circumstances an isotope study using either ^{99m}Tc DMSA or MAG3 is recommended. If function is detected, albeit very poor function, then one is dealing with PUJ; if there is no function then there is little point in a drainage procedure as a totally non-functioning kidney with PUJ never shows function following drainage; whereas a poorly functioning kidney with PUJ may show recovery following drainage. Rarely a cyst puncture with instillation of contrast will distinguish between MDK and PUJ.

On ^{99m}Tc MAG3 studies there is no function of the MDK; the opposite kidney requires assessment for adequate drainage. There is debate as to the need for an MCU if the ultrasound scan of the bladder is normal.

SIMPLE CYSTS

Simple cysts in children are rare and usually detected incidentally. In the largest reported paediatric ultrasound series (16 102 cases), cysts were found in 0.22%.⁶ This was not related to age. The diagnosis of a simple renal cyst should be one of exclusion, especially if the upper pole is involved when one should suspect a duplex kidney or a calyceal cyst or part of another “cystic disease”. Ultrasound cannot differentiate a simple cyst from other pathology; this requires an IVU or magnetic resonance urography. Follow up ultrasound into adolescence is suggested to determine whether other cysts develop.

CALYCEAL CYSTS

This is not a true “cystic” condition but rather an observation made on ultrasound and confirmed on IVU. The importance of a calyceal cyst is the possibility of a calculus developing within or the theoretical existence of TB as the cause. In the context of cystic disease, this needs to be identified as distinct.

MULTILOCULAR CYST/MULTILOCULAR CYSTIC WILMS’ TUMOUR

Multilocular cystic nephroma is a rare cystic renal mass derived from metanephric blastema seen in children. Histology varies from completely benign (multilocular renal cyst) to malignant (multilocular cystic Wilms’ tumour). Clinically the child may present with an abdominal mass. Ultrasound shows a multilocular renal mass with multiple cysts and septations and is non-functioning on isotope. The hallmark is the presence of a capsule around the cysts.⁷ Computed tomography (CT) or magnetic resonance imaging (MRI) scanning should be undertaken in all these children.

LOCALISED CYSTIC DISEASE OF THE KIDNEY

This recently recognised condition is genetically, radiologically, and morphologically distinct from autosomal dominant polycystic



Figure 5 Ultrasound scan of both kidneys taken antenatally. Both kidneys (marked by the × and +) are globally hyperechoic and large. Ultrasound is sensitive in the detection of “bright” kidneys but not specific.

kidney disease (ADPKD). The involved segment is enlarged, and contains multiple small cysts that merge into normal renal parenchyma with no sharp demarcation. There is no surrounding capsule on imaging or histology. This condition differs from ADPKD as it is localised to one part of one kidney.⁸ Some of the earlier reported patients with unilateral ADPKD almost certainly had this condition. Clinically the lesions are not progressive in the few reported cases; as the natural history is unclear the kidney should be followed up. Hypertension has been reported.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney describes an appearance on IVU where dilatation of the collecting ducts causes a medullary blush, in association with calculi. This may be focal or generalised and the kidney may be enlarged; it is rarely seen in childhood. On IVU, the blush seen is related to the calyces, an appearance seen in ARPKD. The term renal tubular ectasia is used to describe these changes.

ACQUIRED CYSTIC RENAL DISEASE

There is no underlying cystic renal disorder, no other organs are involved. Children in chronic renal failure may develop cysts; the frequency increases with length of dialysis with up to 90% developing cysts if on dialysis for more than 10 years. After transplantation the cysts tend to regress in size. Complications include the potential of renal cell carcinoma or haemorrhage. Ultrasound is adequate for diagnosis and follow up.

Genetic cystic disease

Although conveniently divided into dominant, recessive, and cysts associated with syndromes, the imaging is more complex. Similar imaging features may be seen in more than one condition and furthermore the appearances may change with time; these two factors stress a comprehensive imaging work up at presentation as well as at follow up. One cannot rely solely on just ultrasound at diagnosis.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD is characterised both by renal and extrarenal manifestations. It usually presents after the third decade of life but presentation in childhood is recorded. There is variability in the severity of the renal disease when detected in infancy or antenatally.⁹ The estimated prevalence is at least 1/1000. Two and possibly three genetic loci have been identified. Ninety per cent of families have the gene located on the short arm of chromosome 16 (PKD1)¹⁰; the second gene is on chromosome 4 (PKD2). Spontaneous mutation occurs and accounts for lack of family history. In PKD1 families, 64% of affected children under 10 years of age will have cysts; this figure rises to 90% by the age of 19 years.¹¹ In childhood, extrarenal manifestations are rare but include cysts in the liver, pancreas, or spleen,^{12 13} and subarachnoid haemorrhage caused by intracranial aneurysm. Congenital hepatic fibrosis is generally associated with ARPKD but is reported in association with ADPKD.¹⁴

Ultrasound

The prenatal ultrasound may show large hyperechoic kidneys (fig 5) but is not specific (see ARPKD for differential diagnosis). This observation is unexpected and has led to some confusion. In infancy the ultrasonic appearances are variable, from normal to a few isolated cysts, to a kidney packed full of cysts. The more multiple the cysts, the larger the kidneys. The cysts are generally scattered throughout both the cortex and medulla. Frequently there is unequal involvement of the kidneys and the intervening renal tissue appears normal. When found in children (particularly very young children) with no family history, the diagnosis of tuberose sclerosis (TS) must be considered.

Intravenous urography

When the cysts are visible on ultrasound, the IVU will show compression and displacement of calyces (fig 6A) and the renal outlines are lost. The quality of the IVU is usually poor because of the multiplicity of the cysts, and infrequently carried out.

Radiionuclide

A ^{99m}Tc DMSA scan will give information regarding the differential function and will show photon deficient areas occupied by the cysts with uptake in the intervening compressed normal parenchyma (fig 6B).

TUBEROSE SCLEROSIS

Tuberose sclerosis (TS) is an autosomal dominant condition with a reported prevalence of 1 in 10 000 and is characterised by multiple hamartomas in the brain, skin, heart, kidneys, liver, lung, and bone. Genetic linkage has been established to chromosomes 9 and 16; the latter is located in the same region as the ADPKD1 gene. The incidence of renal manifestations varies between 47% and 73%. Angiomyolipomas are found in older patients as they develop and grow in adolescence. They

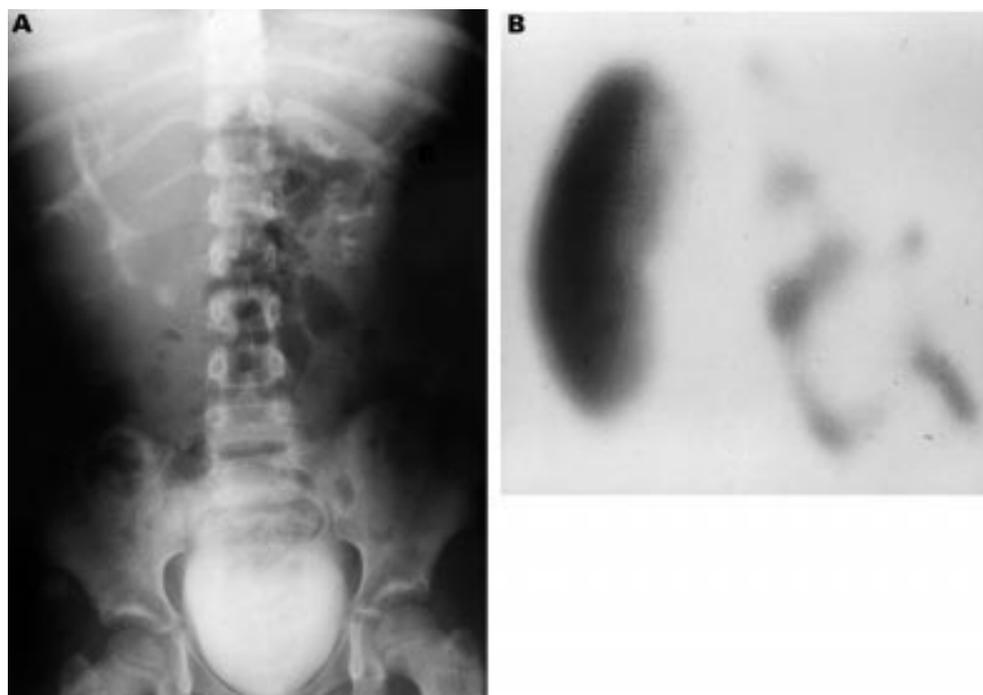


Figure 6 (A) ADPKD. Intravenous urogram on a child with ADPKD. The right kidney is large and the left appears normal showing the asymmetric nature of the condition. The calyces on the right are displaced around the intrarenal cysts. (B) ^{99m}Tc DMSA scan on the same patient showing a normal left kidney. On the right there is a small amount of functioning renal parenchyma around the non-functioning renal cysts.

may occur with or without cysts. Renal cysts are found less frequently (18–53%) and in the younger patients. No imaging modality can currently differentiate the renal TS cysts from ADPKD (fig 7). Echocardiography and cranial CT/MRI should form part of the routine diagnostic work up.¹⁵

Ultrasound

There are two appearances of the kidneys, either multiple cysts or multiple small rounded echogenic foci throughout the parenchyma from angiomyolipomas. Occasionally the cysts and angiomyolipomas may coexist giving a mixed appearance. A rare complication may be haemorrhage. There is a higher incidence of renal cell carcinoma in later life.

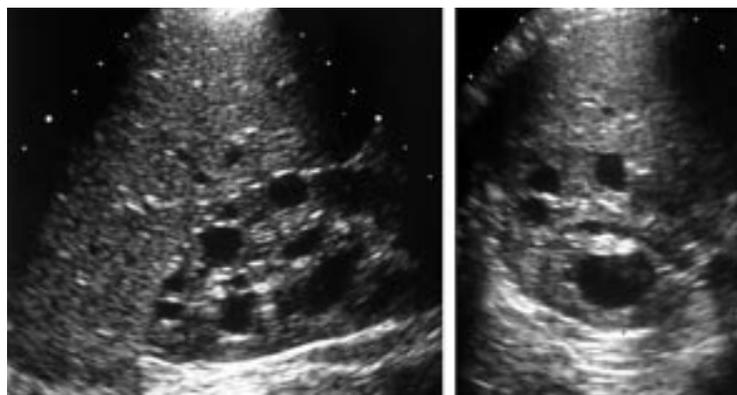


Figure 7 Tuberose sclerosis. Longitudinal and transverse sonogram of the right kidney. The left kidney had similar appearances on ultrasound. The sonogram shows multiple cysts of varying sizes scattered throughout the parenchyma of the kidney. This child's mother had kidneys which looked very similar and she was initially thought to have ADPKD until the diagnosis became apparent with other clinical manifestations of tuberose sclerosis.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

This is a rare genetic disorder with an incidence of approximately 1 in 55 000. The inheritance is recessive; the gene has been located on chromosome 6. All children have hepatic and renal involvement. The liver will show hepatic fibrosis in all children by the time they reach late adolescence; there may also be biliary stasis with changes similar to that seen in Caroli's disease. Splenomegaly is a result of portal hypertension secondary to the hepatic fibrosis. Less severely affected children may present in childhood or even in adolescence.¹⁶

Ultrasound

Prenatal diagnosis has been reported as early as 14–17 weeks gestation. The appearance of bilateral echogenic kidneys during the fetal period is not specific to ARPKD. The differential diagnosis of echogenic kidneys detected antenatally includes ARPKD, ADPKD, dysplasia, malformation syndromes associated with dysplasia, and glomerulocystic kidney disease.

In early infancy both kidneys are equally involved and enlarged (>95th centile). With growth of the child, the kidneys "appear" less enlarged. Typically there is a hyperechoic cortex and medulla; variations include the medulla being brighter than the cortex. With high frequency ultrasound probes, small (1–2 mm) cysts may be detected in the medulla (fig 8A). Occasionally cysts of greater than 2 cm may be found, especially as the child grows. There are well described cases where the imaging is "characteristic" of ARPKD in infancy, yet by 5 years of age the imaging strongly resembles ADPKD.

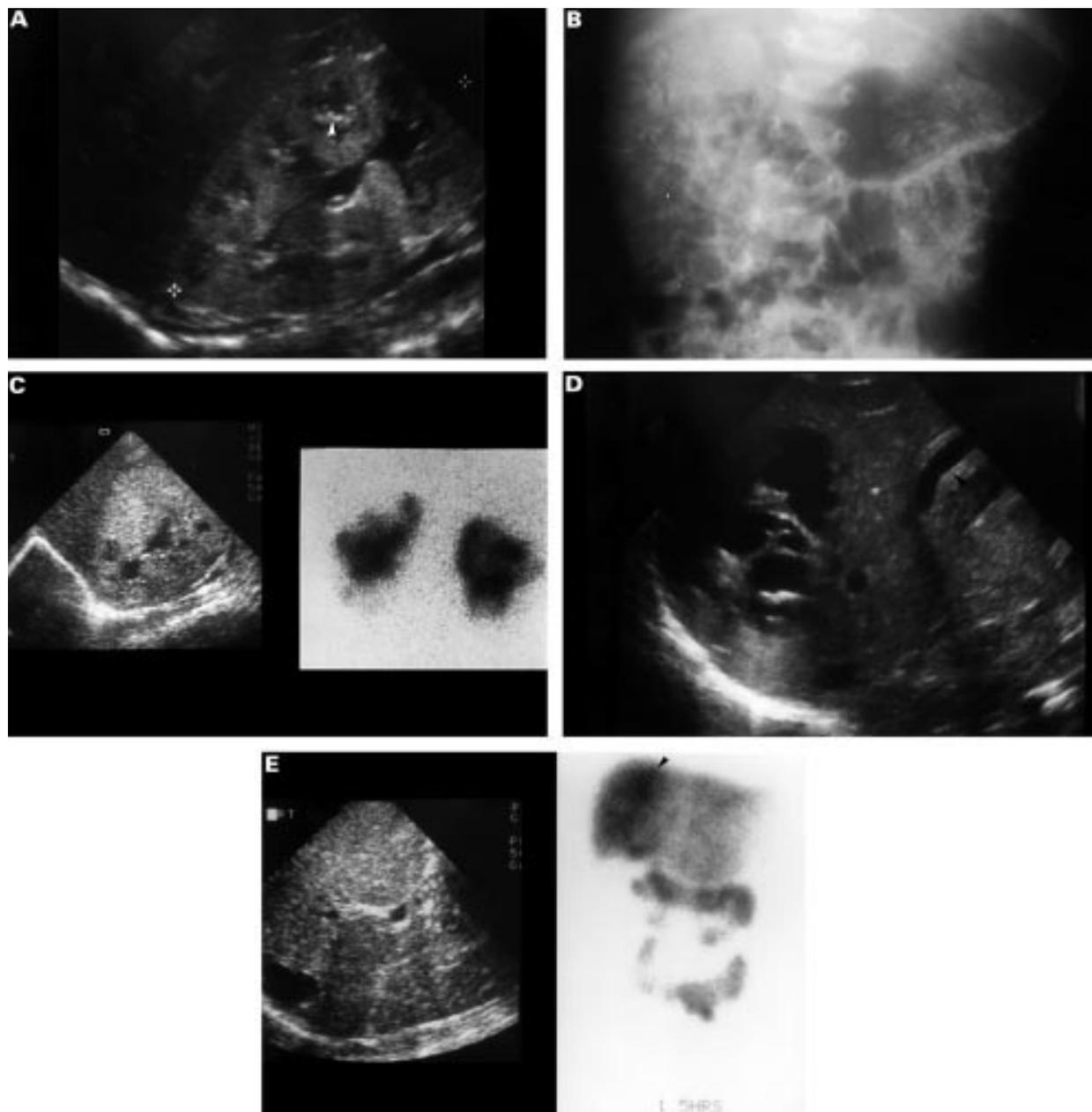


Figure 8 (A) ARPKD—ultrasound scan. Longitudinal supine sonogram of the right kidney. This shows a considerably enlarged kidney (between the + and +) with a globally echogenic echonephrogram. The medullae show a number of echogenic foci (arrow) which is the acoustic enhancement behind the small medullary cysts. (B) ARPKD—intravenous urogram. Two considerably enlarged kidneys with the typical streaky radiating pattern of contrast excretion. (C) ARPKD—ultrasound and ^{99m}Tc DMSA scans. Left image shows the typical large hyperechoic kidney of ARPKD. Right image shows the ^{99m}Tc DMSA scan on the same patient, indicating the focal defects in mainly the polar regions of the kidney. The defects are not related to large cysts as can be seen from the ultrasound scan. This child had not suffered from urinary tract infections. (D) ARPKD—liver ultrasound scan. This longitudinal scan of the liver of the baby in (A) shows multiple cystic dilations of the bile ducts in the liver. The gall bladder is arrowed. (E) ARPKD—liver ultrasound and Hida scans. Left image is a longitudinal scan of the liver, showing a “cyst” high in the right lobe of the liver. Right image is a Hida scan on the same patient. Hida is a radiopharmaceutical which is excreted in the bile. The image shows accumulation of tracer within the “cyst” seen on ultrasound (arrow). Note also the large left lobe of the liver.

Most affected children have some degree of hepatosplenomegaly as they grow. The spectrum of hepatic abnormalities may be subtle on ultrasound. In the young child the liver may be normal or enlarged with increased echogenicity in the periportal region from the bile duct proliferation and fibrosis. Single or multiple cysts communicating and closely related to the biliary tree together with biliary ectasia may be present. A large spleen and evidence of portal hypertension and varices may be shown with ultrasound and Doppler examination.¹⁷

Intravenous urography

The IVU is still considered mandatory to confirm the diagnosis ARPKD. This will show bilateral and symmetrical enlargement of the kidneys and a streaky nephrogram as contrast clears in the ectatic collecting ducts. This may require delayed images up to 24 hours. The IVU should be undertaken at about 3–6 months of age as renal immaturity with or without associated renal impairment before this age may result in non-visualisation of the kidneys (fig 8B). However, infants with ADPKD presenting with large hyperechoic

kidneys in the neonatal period may show “puddling” of contrast to differentiate from ARPKD.¹⁸

Radioisotopes

Renal—^{99m}Tc DMSA studies in ARPKD show patchy uptake of isotope, in particular at the poles. The defects noted are relatively large and do not relate to any focal abnormality seen on ultrasound. These changes were seen in all children from this institution. The changes on ^{99m}Tc DMSA are non-specific; however, in this clinical setting with no history of UTI these defects are specific to ARPKD (fig 8C).

Liver—^{99m}Tc HIDA is a hepatobiliary agent which, following hepatocyte uptake, is secreted into the bile. After 1 year of age, the ^{99m}Tc HIDA scan shows an enlarged left lobe of the liver with delayed passage of isotope through the liver, sometimes with areas of pooling and prominence of the duct system, even when ultrasound fails to show dilatation of the bile ducts (fig 8D). This provides a valuable non-invasive method for the demonstration of subclinical biliary ectasia which is invariable in ARPKD. This appearance has been described in Caroli’s disease (fig 8E).

JUVENILE NEPHRONOPHTHISIS

Juvenile nephronophthisis has an autosomal recessive inheritance and presents in childhood as chronic renal failure. It is characterised by an early concentrating defect, polyuria, polydipsia with growth retardation, and anaemia.

MEDULLARY CYSTIC DISEASE

Medullary cystic disease shows an autosomal dominant inheritance and presents up to the fourth decade of life.

Imaging in juvenile nephronophthisis and medullary cystic disease

As the ultrasound appearances are similar they will be described together. Ultrasound will reveal two normal sized kidneys with a globally hyperechoic appearance. Cysts are not a feature till late in the disease and are then typically corticomedullary. An IVU is of little help because of very poor opacification of the kidneys. In the early stages of the disease when the tubules are affected to a greater degree than the glomeruli, the ^{99m}Tc DMSA scan may fail to show the kidneys, yet the ^{99m}Tc DTPA scan (a glomerular agent) may be almost normal.

Extrarenal manifestations reported in juvenile nephronophthisis include skeletal abnormalities, congenital hepatic fibrosis, and mental retardation.

Conclusion

Cystic renal disease is a wide spectrum of conditions; imaging forms a crucial aspect in the evaluation of the child. The primary imaging modality is ultrasound. However in almost all cases other imaging is required to ensure that the suggested diagnosis or differential diagnosis is as accurate as possible at presentation. Follow up of these children is essential and includes imaging. The screening of family members with ultrasound is a useful procedure and could be undertaken in relevant families. Each patient is unique; imaging should be comprehensive and collation of all the information is essential to have the best chance of reaching a diagnosis.

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