Adult Renal Cystic Disease: A Genetic, Biological, and Developmental Primer

Venkata S. Katabathina, MD • Gopi Kota, MD • Anil K. Dasyam, MD • Alampady K. P. Shanbhogue, MD • Srinivasa R. Prasad, MD

Renal cystic diseases in adults are a heterogeneous group of disorders characterized by the presence of multiple cysts in the kidneys. These diseases may be categorized as hereditary, acquired, or developmental on the basis of their pathogenesis. Hereditary conditions include autosomal dominant polycystic kidney disease, medullary cystic kidney disease, von Hippel-Lindau disease, and tuberous sclerosis. Acquired conditions include cystic kidney disease, which develops in patients with end-stage renal disease. Developmental cystic diseases of the adult kidney include localized renal cystic disease, multicystic dysplastic kidney, and medullary sponge kidney. In recent years, many molecular and cellular mechanisms involved in the pathogenesis of renal cystic diseases have been identified. Hereditary renal cystic diseases are characterized by genetic mutations that lead to defects in the structure and function of the primary cilia of renal tubular epithelial cells, abnormal proliferation of tubular epithelium, and increased fluid secretion, all of which ultimately result in the development of renal cysts. A better understanding of these pathophysiologic mechanisms is now providing the basis for the development of more targeted therapeutic drugs for some of these disorders. Cross-sectional imaging provides useful information for diagnosis, surveillance, prognostication, and evaluation of treatment response in renal cystic diseases.
Introduction
Renal cystic disease, a common cause of end-stage renal disease in adults, comprises a wide spectrum of hereditary, acquired, and developmental conditions (Table 1). Recent advances in cytogenetics and molecular biology have provided unique insights into fundamental processes involved in the pathogenesis of a number of renal cystic diseases in adults. Inherited cystic diseases are linked to various genes involved in the formation and functioning of the primary cilia of the renal tubular epithelium. Dysfunction of the renal primary cilia leads to epithelial proliferation and the development of renal cysts. Nonhereditary renal cystic diseases are secondary to obstructive, stromal-epithelial malinductive, and neoplastic mechanisms. Although the focus of this review is on adult renal cystic diseases, there is some overlap with pediatric diseases that manifest with kidney cysts. Common causes of renal cystic disease in children include autosomal recessive polycystic kidney disease, multicystic dysplastic kidney, nephropthisis, and glomerulocystic kidney disease. In addition, renal cysts in children may develop in the presence of hereditary conditions such as von Hippel-Lindau disease, tuberous sclerosis, Bardet-Biedl syndrome, oral-facial-digital syndrome, and Meckel-Gruber syndrome. Although some children with these disorders survive into adulthood, many die of kidney disease and its attendant complications. Better understanding of cytogenetic and pathophysiologic mechanisms has led to the development of new options for treating some of these diseases. Advances in cross-sectional imaging studies, such as renal volumetry performed with magnetic resonance (MR) imaging, are helpful for evaluating the efficacy of new drugs and monitoring disease progression.

The article describes recent advances in the genetics, pathophysiology, and molecular biology of renal cystic diseases in adults, reviews pertinent imaging findings, and discusses their implications for diagnosis and management (Tables 2, 3).

Renal Cilia and Renal Cystic Diseases
The primary cilium of the renal tubular epithelial cell is a fine (approximately 0.25 μm in cross-sectional diameter) microtubular non-motile organelle that emanates from the cell surface. It plays a fundamental role in renal tubule organization and function. Each cilium consists of nine circumferentially arranged doublet microtubules that are enclosed by an extension of the cell membrane (Fig 1) (1,2). In comparison with motile cilia found elsewhere in the body, renal primary cilia lack the central pair of singlet microtubules and no central microtubules (so-called 9 + 0 configuration) enclosed within the cell membrane.

Table 1
Select Renal Cystic Diseases in Adults

<table>
<thead>
<tr>
<th>Hereditary diseases</th>
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<tbody>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
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<tr>
<td>Medullary cystic kidney disease</td>
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<tr>
<td>Von Hippel-Lindau disease</td>
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<tr>
<td>Tuberous sclerosis complex</td>
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<tr>
<td>Nonhereditary diseases</td>
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<tr>
<td>Acquired cystic kidney disease</td>
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<tr>
<td>Medullary sponge kidney</td>
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<tr>
<td>Multicystic dysplastic kidney</td>
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<tr>
<td>Localized renal cystic disease</td>
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Figure 1. Drawing shows the cross-sectional appearance of the renal primary cilium, with nine circumferentially arranged doublet microtubules (arrows) and no central microtubules (so-called 9 + 0 configuration) enclosed within the cell membrane.
the cell that regulate tissue development and homeostasis (3). In addition to polycystin-1 and polycystin-2, many other proteins (eg, nephrocystin, fibrocystin, polaris, Bardet-Biedl syndrome, and oral-facial-digital syndrome proteins) are localized to the surface of the cilium (4). Abnormality of these proteins, with resultant ciliary dysfunction, is a universal characteristic of inherited renal cystic diseases, which are discussed in the next section.

Table 2
Cytogenetic, Pathophysiologic, and Imaging Characteristics of Hereditary Renal Cystic Diseases in Adults

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Gene, Chromosome, Protein</th>
<th>Pathophysiologic Features</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>PKD1, 16p13, polycystin-1; PKD2, 4q21, polycystin-2</td>
<td>Deranged function of renal cilium with increased proliferation of renal tubular epithelium and increased fluid secretion</td>
<td>Bilateral enlarged kidneys with multiple expansile cysts</td>
</tr>
<tr>
<td>Medullary cystic kidney disease</td>
<td>MCKD1, 1q21, unknown; MCKD2, 16p12, uromodulin</td>
<td>Exact pathogenesis uncertain; ciliary dysfunction believed to be secondary to altered interaction of MCKD-1 or MCKD-2 protein with nephrocystin</td>
<td>Multiple cysts at the corticomedullary junction and in the medulla</td>
</tr>
<tr>
<td>Von Hippel-Lindau disease</td>
<td>VHL, 3p25-26, pVHL</td>
<td>Upregulation of HIF with resultant increase in its downstream effectors; derangement of ciliary assembly and mechanosensory function of renal cilium</td>
<td>Multiple, variably sized cysts in both kidneys; multiple interspersed cystic and solid renal cell carcinomas</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSG2, 16p13, tuberin; TSC1, 9q34, hamartin</td>
<td>Uncontrolled activation of mTOR and its downstream effectors; defects in ciliary function and epithelial cell polarity</td>
<td>Multiple, bilateral renal cysts intermixed with multiple angiomyolipomas</td>
</tr>
</tbody>
</table>

Note.—HIF = hypoxia-inducible factor, mTOR = mammalian target of rapamycin.

Table 3
Pathophysiologic and Imaging Characteristics of Nonhereditary Renal Cystic Diseases in Adults

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Pathophysiologic Characteristics</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired cystic kidney disease</td>
<td>Hyperplasia of tubular epithelium because of increase in mitogenic growth factors and activation of proto-oncogenes with increased fluid secretion</td>
<td>Bilateral small kidneys with multiple cysts, increased risk of intracystic hemorrhage, and development of renal cell carcinomas</td>
</tr>
<tr>
<td>Medullary sponge kidney</td>
<td>Disruption of the embryonic interface between the developing ureteral bud and the metanephric blastema during embryogenesis</td>
<td>Medullary nephrocalcinosis and cysts, paintbrushlike appearance at urography, multiple renal calculi</td>
</tr>
<tr>
<td>Multicystic dysplastic kidney</td>
<td>Abnormal metanephric-mesenchymal differentiation in the setting of urinary tract obstruction during embryogenesis</td>
<td>Nonreniform, nonfunctional kidney with multiple peripheral cysts and central solid components</td>
</tr>
<tr>
<td>Localized renal cystic disease</td>
<td>Pathogenesis is unclear, but an acquired maldevelopmental origin is hypothesized</td>
<td>Conglomerate mass of multiple simple cysts of various sizes, separated by enhancing or atrophic renal tissue and without a definite capsule</td>
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Hereditary Renal Cystic Diseases

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease, the most common hereditary renal cystic disease, is characterized by bilaterally enlarged kidneys with multiple expansile cysts (5). This disease occurs in one of 400–1000 live births and affects approximately 300,000 to 600,000 Americans, showing no predilection for a particular sex or race (5,6). Autosomal dominant polycystic kidney disease is the third most common cause of end-stage renal disease and affects 5%–10% of patients undergoing dialysis (5). In most of these patients, the disease originated through autosomal dominant inheritance. In 5%–10% of cases, the disease is due to a spontaneous mutation and there is no family history (7).

The disease may arise from mutations in two genes, which are known as \( PKD1 \) and \( PKD2 \). Mutations in \( PKD1 \), which is located on the short arm of chromosome 16 (at 16p13) and encodes the protein polycystin-1, account for about 85% of cases. Mutations in \( PKD2 \), which is located on the long arm of chromosome 4 (at 4q21) and encodes the protein polycystin-2, are responsible for approximately 15% of cases (7,8). Patients with \( PKD1 \) mutations have more severe disease than those with \( PKD2 \) mutations. Polycystin-1 and polycystin-2 proteins are localized within the cell membrane of the primary cilia of renal tubular epithelial cells (4). They play an important role in tissue development and homeostasis by regulating intracellular calcium transport (3). In addition, they are involved in cell-cell and cell-matrix interactions that determine tubular morphogenesis. Deranged function of these proteins leads to overproliferation of tubular epithelial cells, increased intratubular fluid secretion, and altered interaction between basement membrane and extracellular matrix (5). All these changes eventually lead to tubular ectasia and cyst formation. Increased proliferation of the renal tubular epithelium is caused by overexpression of epidermal growth factor receptor on the epithelial lining of the cyst. Cyclic adenosine monophosphate, acting as a second messenger, also exerts a strong proliferative effect on the renal tubular epithelium (8). Fluid secretion increases because of the mislocalization of sodium-potassium-activated adenosine triphosphatase to the apical membrane of the tubular epithelium and the resultant secretion of sodium ions, which produces a gradient that leads to further fluid secretion and cystic expansion (8). Overexpression of cystic fibrosis transmembrane conductance receptor, a chloride channel, also may lead to increased fluid secretion (8).

The renal cysts in autosomal dominant polycystic kidney disease involve only 1%–2% of nephrons and may develop from any segment of the nephron (5). According to Knudson’s “two-hit” hypothesis (9), all renal tubular epithelial cells harbor germ-line mutations in \( PKD1 \) and \( PKD2 \). If a somatic mutation occurs in the normal allele (the “second hit”) in a particular epithelial cell, monoclonal proliferation of that cell will take place, accompanied by an increase in fluid secretion, with resultant cyst formation (Fig 2). Intrarenal ischemia caused by continued renal cyst expansion with resultant activation of the renin-angiotensin-aldosterone system leads to hypertension. At gross pathologic analysis, bilateral renal enlargement is seen with multiple cysts of various sizes. At histologic analysis, the cysts are lined by columnar to cuboid to flattened epithelium and are surrounded by a thick basement membrane (5).
Autosomal dominant polycystic kidney disease. (a) Coronal T2-weighted MR image shows enlargement of both kidneys with multiple expansile renal cysts (arrows), as well as multiple hepatic cysts (arrowheads). (b) Axial T2-weighted fat-saturated MR image obtained in another patient shows similar enlargement of the kidneys, with multiple cysts (arrows).

Figure 3. Autosomal dominant polycystic kidney disease. (a) Coronal T2-weighted MR image shows enlargement of both kidneys with multiple expansile renal cysts (arrows), as well as multiple hepatic cysts (arrowheads). (b) Axial T2-weighted fat-saturated MR image obtained in another patient shows similar enlargement of the kidneys, with multiple cysts (arrows).

Imaging plays an important role in the diagnosis and management of autosomal dominant polycystic kidney disease, detection of complications, and assessment of disease progression or treatment response (6,10). At cross-sectional imaging, autosomal dominant polycystic kidney disease is characterized by enlargement of both kidneys with innumerable cysts of varied size (Fig 3). Most patients with this disease develop renal cysts by the age of 30 years; however, cysts develop in utero or in the neonatal period in some patients (7). With the progressive growth of cysts over time, a kidney affected by this disease eventually may reach a weight of 8 kg and a length of 40 cm (10). The cysts, most of which have a diameter of 3 cm or more, are distributed diffusely throughout both kidneys (5). Cyst-associated complications such as infection, hemorrhage, and, rarely, cyst rupture, also may be identified at cross-sectional imaging. Patients with autosomal dominant polycystic kidney disease do not have an increased risk for renal cell carcinoma (5). However, about 45% develop end-stage renal disease—the most common cause of mortality and morbidity—by the age of 60 years. Extrarenal manifestations of the disease include hepatic, pancreatic, seminal vesicle, and splenic cysts; intracranial arterial aneurysms; aortic aneurysms; abdominal wall hernias; colonic diverticula; and aortic and mitral valve abnormalities (Fig 3a).

A study by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease was funded and established by the National Institutes of Health to develop methods for reliably measuring the progression of autosomal dominant polycystic kidney disease (11). MR imaging–based renal and cyst volumetry allows the assessment of renal and cyst volumes, which may be used as indicators of disease progression or treatment response (11). With this technique, coronal unenhanced T1-weighted, coronal T2-weighted, and coronal gadolinium–enhanced T1-weighted images are acquired with a section thickness of 3 mm (12). The total kidney volume then is calculated by using a stereologic method: The area of the kidney measured on each section in the set of contiguous images is multiplied by the section thickness, and the products are then summed (12). (Stereology is a body of mathematical methods used to calculate three-dimensional parameters of a structure, such as volume, surface area, and total curvature, from two-dimensional measurements obtained on cross-sectional images of that structure.) Patients with autosomal dominant polycystic kidney disease have a mean renal volume of more than 1000 mL (the normal mean is 150 mL) and an age-related increase in total renal volume and total cyst volume, with a mean annual increase of 63.4 mL in renal volume (11,12). In addition, hypertension, gross hematuria, and abdominal pain may develop and the glomerular filtration rate may decline in association with increasing kidney volumes and increasing rates of kidney growth (13,14). Overall increases in renal and cyst volumes are indicative of progression of the disease.
MR imaging also allows accurate estimation of renal blood flow. In patients with autosomal dominant polycystic kidney disease, a reduction in renal blood flow parallels the increase in total kidney volume, precedes a decline in growth factor receptor levels, and is predictive of structural and functional disease progression (15).

Medullary Cystic Kidney Disease
Medullary cystic kidney disease is a rare inherited renal disorder characterized by multiple medullary cysts and tubular-interstitial nephropathy in kidneys that are small to normal in size. The disorder is acquired through autosomal dominant inheritance and eventually leads to end-stage renal disease (7,8). Two forms of medullary cystic kidney disease have been identified: type 1, which is caused by mutations in the MCKD1 gene on chromosome 1 (at 1q21), whose protein product has not yet been identified; and type 2, which is due to mutations in the MCKD2 gene on chromosome 16 (at 16p12), which encodes uromodulin (Tamm-Horsfall glycoprotein) (8). The exact functions of the MCKD1 and MCKD2 gene products are unclear; however, it is hypothesized that they may interact with nephrocystin and other binding proteins to form focal adhesion signaling complexes in renal tubules (16). Nephrocystin is localized to the renal cilium and helps in cell-cell and cell-matrix interactions through association with signaling molecules involved in cell adhesion (16–18). Deranged function of all these proteins may result in ciliary dysfunction and development of multiple medullary cysts (17). At histologic analysis, atrophy of renal tubules is seen with medullary cysts and interstitial cell infiltration associated with fibrosis (8).

Clinically, patients with medullary cystic kidney disease present with polyuria and polydipsia secondary to urinary concentration defects and salt wasting. They also tend to develop hyperuricemia and gout (8). In many cases, the disease progression is gradual: In patients with type 1 disease, end-stage disease develops between the ages of 50 and 70 years (median age, 62 years); in those with type 2 disease, end-stage disease develops between the ages of 20 and 60 years (median age, 32 years) (16).

The diagnosis of medullary cystic kidney disease is mainly based on clinical features and a thorough review of family history. The presence of medullary cysts supports the diagnosis but is not essential (19). At imaging, bilateral normal-to small-sized kidneys with multiple cysts (of size less than 3 cm) at the corticomedullary junction and in the renal medulla may be seen (20,21). Ultrasonography (US) is the modality of choice for the initial imaging evaluation. MR imaging may be recommended as a second-line examination when the findings at US are indeterminate (21). The differential diagnosis includes medullary sponge kidney, multicystic dysplastic kidney, and lithium-induced renal disease. Characteristic clinical findings and the typical location of cysts in the renal medulla help differentiate medullary cystic disease from other renal cystic diseases. Renal transplantation is the treatment of choice; medullary cystic kidney disease does not recur in the transplanted kidney (22).

Von Hippel-Lindau Disease
Von Hippel-Lindau disease is a rare autosomal dominant disorder characterized by the development of cysts, cystic neoplasms, and hypervascular tumors in the visceral organs. Its estimated prevalence worldwide is one of 30,000–50,000
Von Hippel-Lindau disease. Axial image from contrast material–enhanced computed tomography (CT) depicts multiple cysts in both kidneys (arrows) and an enhancing mass in the right kidney (arrowhead). The mass has attenuation similar to that in soft tissue, a finding suggestive of clear cell renal cell carcinoma.

persons in the general population, with 6000–7000 affected in the United States alone (23). Males and females are affected equally. Renal lesions, including renal cysts and renal cell carcinomas, are seen in 30%–75% of cases. Renal cysts develop in 59%–63% of patients, and renal cell carcinomas are reported to occur in 24%–45% (24). Extrarenal manifestations include central nervous system hemangioblastomas, pancreatic cysts, serous cystadenomas, neuroendocrine tumors, pheochromocytomas, and papillary cystadenomas of the epididymis in male patients (25). Clinically, cases of von Hippel-Lindau disease are classified as type 1 when a pheochromocytoma is present or type 2 when no pheochromocytoma is present. Type 2 disease is further differentiated as type 2A (pheochromocytoma with central nervous system hemangioblastoma but without renal cell carcinoma), type 2B (pheochromocytoma with both renal cell carcinoma and central nervous system tumors), or type 2C (pheochromocytoma alone) (26).

Von Hippel-Lindau disease is a result of inactivating mutations of the VHL tumor-suppressor gene located on chromosome 3 (at 3p25–p26), which encodes the protein pVHL. The high penetrance of the VHL gene leads to an early onset of disease (at the age of 18–30 years) and high frequency of clinical manifestations (approximately 90% at 60 years) (5). The pVHL protein is primarily involved in proteasomal degradation of HIF, a tetrameric protein that is a critical component of oxygen sensing and homeostasis mechanisms. Hypoxic conditions cause an intracellular accumulation of HIF with downstream activation of hypoxia response genes that eventually restore the oxygen balance. In patients with von Hippel-Lindau disease, there is uninhibited upregulation of HIF and its downstream effectors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF) α, even in the absence of hypoxia. The increased levels of growth factors spur the development of hypervascular tumors in multiple organs and renal cysts (Fig 4) (26). Recent studies have indicated that the pVHL protein plays a central role in renal ciliogenesis, ciliary assembly, and mechano-sensory function of the cilium (27). The pVHL protein thus has profound effects on the growth and differentiation of renal tubular epithelial cells generally; derangements in its production result in abnormal proliferation of renal epithelium, which leads to renal cyst formation (28).

At gross pathologic analysis, the kidneys appear normal in weight and size because most of the cysts and renal cell carcinomas are small (5). At histologic analysis, four different types of renal lesions may be seen: benign cysts, atypical cysts, cystic renal cell carcinomas, and solid renal cell carcinomas. All these lesion types include a variable number of clear cells as a component (5).

At imaging, multiple cysts of various sizes are seen bilaterally in the kidneys and are interspersed with complex cystic or solid hypervascular masses (Fig 5). Neoplastic cysts may show wall thickening and enhancing solid mural components (24,25). Clear cell renal cell carcinomas are the leading cause of mortality and morbidity in patients with von Hippel-Lindau disease, especially those with disease types 1 and 2B (29). An abnormal increase in the HIF level plays a causal role in the development of von Hippel-Lindau–associated clear cell renal cell carcinomas. The natural history of renal lesions in patients with von Hippel-Lindau disease is variable, with some cysts undergoing involution over time, and others, gradual enlargement. Complex cysts and solid renal lesions may show uniform enlargement (30). In addition, progression of simple cysts in cystic renal cell carcinoma has been described, but there is no correlation between the size or the number of cysts and their malignant potential (24). Current recommendations for the treatment of renal lesions in von Hippel-Lindau disease include follow-up imaging at 6- to 12-month intervals for tumors with a maximal diameter of less than 3 cm and definitive treatment of those measuring more than 3 cm.
Treatment options include nephron-sparing surgery, radiofrequency ablation, and cryoablation. Intraoperative US may be helpful for identifying resectable lesions.

**Tuberous Sclerosis Complex**

Also referred to as Bourneville disease, tuberous sclerosis complex is an autosomal dominant multisystem disorder characterized by seizures, mental retardation, and hamartomas in various organs of the body. Its prevalence in the general population is approximately one of 10,000. Fifty to sixty percent of cases are sporadic, occurring in patients with no family history of the disease (32). Renal manifestations, which are seen in 50%–60% of patients, include angiomyolipomas (34%–80% of cases) and renal cysts (14%–32% of cases) (33). Common extrarenal manifestations include lesions of the central nervous system (eg, cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and white matter abnormalities), heart (rhabdomyomas), lungs (lymphangioleiomyomatosis), gastrointestinal tract (intestinal polyps), hepatobiliary system (hepatic angiomylipomas), skeleton (multiple cystlike lesions and sclerotic foci), and retroperitoneum (lymphangioleiomyomatosis) (34).

Tuberous sclerosis complex results from inactivating mutations in either the *TSC1* or the *TSC2* gene. *TSC2* is located at 16p13 and encodes for the protein tuberin. *TSC1* is located at 9q34 and encodes for the protein hamartin (33,35). Tuberin and hamartin interact directly to form a cytoplasmic protein complex called tuberin-hamartin, which is normally present in organs such as the kidneys, brain, lungs, and pancreas and is activated by hypoxia. This protein complex functions as a tumor suppressor by inhibiting mTOR and thus plays an important role in controlling cell growth and proliferation (32). In addition, the tuberin-hamartin complex may affect the cell structure and inhibit proliferation by interacting with various intracellular proteins (32). In patients with tuberous sclerosis complex, there is dysregulated activation of mTOR and its downstream effectors because of a decrease in the inhibitory effects of tuberin-hamartin complex, with a consequent increase in protein synthesis and cell growth (Fig 6) (32,35). Data from recent studies have confirmed the existence of an mTOR-independent pathway for renal cystogenesis (36,37). Hamartin is typically localized to the basal body of the renal cilium; inactivation of the tuberin-hamartin complex is thought to result in ciliary dysfunction and defects in cell polarity, which lead to renal cyst formation (37).

A related condition, known as tuberous sclerosis complex 2–polycystic kidney disease 1 syndrome, is characterized by mutations in the genes *TSC2* and *PKD1*, which are located contiguously on chromosome 16, at 16p13.3 (38). Patients with this syndrome have lesions that are characteristic of both tuberous sclerosis complex and polycystic kidney disease, including bilateral enlargement of the kidneys, with renal cystic changes, multiple angiomylipomas, hepatic cysts, intracranial aneurysms, and lymphangioleiomyomatosis.

In patients with tuberous sclerosis complex, cysts may arise in any segment of the nephron, including the glomeruli. The cysts are lined by granular eosinophilic cells with large nuclei. Focal hyperplasia of granular cells produces intraluminal papillary excrescences, which are pathognomonic (5).
Figure 7. Tuberous sclerosis complex. Axial contrast-enhanced CT image shows multiple cysts in both kidneys (arrowheads) in a patient with diagnosed tuberous sclerosis.

At imaging, multiple renal cysts intermingled with angiomyolipomas in both kidneys are characteristic features of tuberous sclerosis complex (Fig 7) (9,34). Both angiomyolipomas and renal cysts may manifest during childhood and tend to increase in size and number with increasing age (39). The overall incidence of renal cell carcinoma among patients with tuberous sclerosis complex is similar to that in the general population, with a lifetime risk of 2%-3% (35,40). However, renal cell carcinoma manifests at an earlier age in patients with tuberous sclerosis complex (mean age, 28 years) than in the general population (mean age, 53 years) and shows greater histologic variety, with clear cell, papillary, and chromophobe subtypes (34,35).

Acquired Renal Cystic Diseases

Acquired cystic kidney disease is defined by the presence of multiple renal cysts (three or more per kidney) in a patient with end-stage kidney disease due to a cause other than hereditary renal cystic disease (41). Between 8% and 13% of patients with end-stage kidney disease have acquired cystic kidney disease before undergoing dialysis (41). Approximately 50% of patients undergoing dialysis have acquired cystic kidney disease, but the percentage varies in accordance with the duration of dialysis. The disease is found in approximately 13%, 50%, and 87% of patients after 2, 6, and 9 years of dialysis, and in nearly 100% of patients after 10 years of dialysis (5). It occurs in male patients with a frequency three times that in female patients, but no correlation has been found between disease incidence and patient age, race, dialysis method, or cause of renal failure (5).

Progressive destruction of functioning renal tissue, with compensatory hypertrophy of remaining nephrons, initiates the disease process. Hyperplasia of renal tubular epithelium is caused by mitogenic factors such as electrolyte imbalances, diminished proton excretion, and hormonal stimuli. In addition, increasing levels of growth factors and activation of proto-oncogenes such as c-ERBB2 are thought to play an active role in pathogenesis (42). Fluid accumulation is probably secondary to tubular obstruction caused by interstitial fibrosis, hyperplastic epithelium, and oxalate crystal deposition. In addition, increased transepithelial fluid secretion may be due to increases in parathyroid hormone, secretin, vasoactive intestinal peptide, and vasopressin levels (42,43). All these abnormalities lead to expansion of the renal tubule, fluid accumulation, and resultant cyst formation (Fig 8).

At gross pathologic analysis, kidneys affected by acquired cystic disease are smaller than normal kidneys and contain multiple cysts of varied size and number. At histologic analysis, cysts are lined by a single layer of epithelium. Hyperplastic and dysplastic changes are not uncommon, with papillary proliferations and papillary adenomas (5). Cysts may show luminal deposition of calcium oxalates and blood products.
At US, small echogenic kidneys with multiple renal cysts are seen bilaterally. At CT and MR imaging, markedly atrophic kidneys with multiple cysts of varying sizes are identified (Fig 9). Cross-sectional imaging studies are helpful not only for diagnosis but also for identifying complications (41). The use of intravenous contrast material is necessary to depict associated renal cell carcinomas. In general, CT or MR imaging is used to detect complications and perform follow-up evaluations, whereas US is more suitable for screening (41).

Complications of acquired cystic kidney disease include bleeding into cysts, cyst infection, ureteral stones, and malignancy. Hemorrhage into renal cysts is a common complication; it occurs in approximately 50% of patients (41,43). Severe bleeding may result in cyst rupture, perinephric hematoma, and retroperitoneal hemorrhage (Fig 10). Approximately 3%–7% of patients develop renal tumors (44). Activation of growth factors and proto-oncogenes such as c-ERBB2 may predispose this group of patients to renal tumors. Risk factors for the development of malignancy include increasing duration of dialysis, male sex, and kidney weight of more than 150 g (5). Two unique histologic subtypes of renal cell carcinoma have been identified in patients with acquired cystic kidney disease: (a) acquired cystic disease–associated renal cell carcinoma and (b) clear cell papillary renal cell carcinoma of the end-stage kidneys (44). Although renal cell carcinomas are a dreaded complication of this disease, they are an unusual cause of death when compared with other causes of renal failure (diabetes mellitus, hypertension, and systemic diseases) (41). Acquired cystic disease–associated renal cell carcinoma is the most common and most aggressive of the two subtypes (44).

Asymptomatic patients may be monitored with follow-up US, whereas complications such as intractable bleeding and solid renal tumors may require nephrectomy. After kidney transplantation, renal cysts in the native kidney often regress; however, renal tumors in the native kidney tend to show more aggressive behavior and may metastasize because of the lowered immune status of the transplant recipient (41).
Medullary Sponge Kidney
Also known as Lenarduzzi-Cacchi-Ricci disease, medullary sponge kidney is a congenital developmental abnormality characterized by ectasia and cystic dilatation of the intrapyramidal or intrapapillary portions of the renal medullary collecting ducts (45). The disease was first described by Lenarduzzi in 1931 (45). Its estimated prevalence in the general population is one of 5000 persons (46). Among patients with calcific kidney stones, 12%–20% have medullary sponge kidney, and an incidence of 0.5% has been reported among patients undergoing excretory urography (47). Most cases are sporadic; however, familial cases with autosomal dominant inheritance also have been described (48).

The exact pathogenesis of medullary sponge kidney is unclear. A disruption in the ureteric bud–metanephros interface during embryogenesis is the hypothesized cause (49). During embryogenesis, the metanephric blastema synthesizes the chemotactic glia-derived neurotrophic factor (GDNF) to attract the ureteric bud, and the ureteric bud tip expresses a GDNF receptor known as RET. GDNF-RET binding is crucial for the formation of ureters and collecting ducts and for nephrogenesis. It is hypothesized that disruption of this mechanism results in medullary sponge kidney (Fig 11) (45,49). Congenital hemihypertrophy, Beckwith-Wiedemann syndrome, Caroli syndrome, Wilms tumor, and horseshoe kidney may be associated with medullary sponge kidney (50). At histologic analysis, ectasia of the medullary and papillary collecting ducts is seen with small cysts (less than 1 cm in diameter) in the medulla. These cysts are usually lined by cuboidal, columnar, or transitional epithelium.

Most patients with medullary sponge kidney are asymptomatic; the kidney condition is often detected incidentally at intravenous urography performed for another reason. In symptomatic patients, hematuria, renal colic, fever, and dysuria are common. Medullary sponge kidney is usually detected in the 3rd to 5th decade of life. Complications such as nephrolithiasis, renal calculi, and urinary tract infection may be seen (45). Patients are prone to renal calculi because of urinary stasis, hypercalciuria, acidification defects, and distal renal tubular acidosis (45).

At US, an echogenic appearance of the medullary pyramids is characteristic of medullary sponge kidney. At intravenous urography, a classic paintbrushlike appearance or papillary blush due to the pooling of contrast material within the dilated medullary collecting ducts may be identified (Fig 12) (47,51). In severe cases, a striated or beaded appearance of the medullary collecting ducts may be seen with resultant distortion of the calices. Both kidneys are usually involved in the disease process, but unilateral or segmental involvement also may be seen. Multidetector CT urography may show a characteristic papillary blush and associated calculi within the dilated collecting ducts (51). Multidetector CT urography has higher sensitivity than intravenous
Multicystic Dysplastic Kidney Disease

Multicystic dysplastic kidney disease is a form of renal dysplasia that is secondary to altered metanephric differentiation during embryogenesis (5). This nonheritable developmental disorder occurs with an incidence of approximately one in 4300 live births (5). Its pathogenesis is unclear; however, it has been postulated that a urinary tract obstruction during embryogenesis may cause failure of the ureteric bud to integrate and branch into the metanephros, with abnormal metanephric differentiation resulting in the development of various congenital anomalies in the kidney and urinary tract, including a multicystic dysplastic kidney (Fig 13) (55). Most cases of multicystic dysplastic kidney disease are sporadic, but a familial form has been described (56).

A multicystic dysplastic kidney is commonly associated with vesicoureteral reflux in the contralateral kidney and with a posterior location of the urethral valves. It is usually detected at birth and regresses during infancy in about two-thirds of patients. Patients with nonregression may present in adulthood with a cystic renal mass. A segmental form of the disease, which commonly involves the upper pole of a duplex kidney, also may be seen with an associated ureterocele at the end of an atretic ureter (57).

The gross appearance of the dysplastic kidney may vary from a small hypoplastic mass to a large nonreniform multicystic lesion resembling a bunch of grapes (7). At histologic analysis, multiple epithelium-lined cysts are seen at the periphery of the kidney, with central solid components that contain cartilage, undifferentiated mesenchyme, immature glomeruli, and primitive tubules (5,7). The pelvicaliceal system, ureter, and renal vessels either are not seen or are severely atrophic.

The imaging appearance of a multicystic dysplastic kidney depends on the age of the patient. An enlarged nonreniform kidney that contains multiple noncommunicating cysts without functioning renal parenchyma is typically seen in children with the disease (57). A few patients present in adulthood with imaging findings of a multiloculated cystic mass with an appearance suggestive of a cystic renal neoplasm. The key findings of multicystic dysplastic kidney disease are a nonfunctioning kidney; peripherally located cysts combined with a central region of solid tissue; and nonvisualization of the renal vessels, pelvicaliceal system, and ipsilateral ureter (Fig 14). Voiding cystourethrography may be helpful for assessing associated vesicoureteral reflux and functioning of the posterior urethral valves. The disease course is typically benign, with the affected kidney tending toward involution over time (58).
Localized Renal Cystic Disease

Also known as segmental renal cystic disease and unilateral renal cystic disease, localized renal cystic disease is a rare, nonhereditary, nonprogressive condition that is characterized by multiple cysts in one kidney, with no cysts in the other kidney or other organs. Many patients are asymptomatic. Among those who are symptomatic, the most common symptoms include abdominal pain, hematuria, and hypertension without impairment of renal function. The pathogenesis of localized renal cystic disease is unclear, but an acquired maldevelopmental origin is hypothesized (7,59). At gross examination, a multicystic lesion composed of cysts of various sizes and separated by normal (or atrophic) renal parenchyma, without a definite capsule, is seen (59). At microscopy, the cysts are lined by flattened epithelium (59).

At cross-sectional imaging, localized renal cystic disease may appear as a conglomerate mass of multiple simple cysts of various sizes, separated by enhancing or atrophic renal tissue, without a definite capsule (Fig 15) (60,61). Cysts may involve the entire kidney or be limited to a portion of the kidney. Typically, the involved kidney shows normal excretion after contrast material administration. The differential diagnosis includes autosomal dominant polycystic kidney disease, multicystic dysplastic kidney, and cystic neoplasms. Unilateral localization, negative family history, and absence of cysts in other visceral organs help differentiate this condition from autosomal dominant polycystic kidney disease, whereas the presence of an intact pelvicaliceal system and renal vessels helps differentiate localized renal cystic disease from multicystic dysplastic kidney. The thick, enhancing septa of cystic renal tumors may be confused with the normal, insinuated renal parenchyma of localized renal cystic disease; however, an evaluation of the entire length of the kidney in the coronal plane is often helpful for differentiating between these two conditions (62). Localized renal cystic disease is a benign condition that requires follow-up with functional imaging studies and surveillance (59,60).

Targeted Therapies for Hereditary Renal Cystic Diseases

Recent advances in our understanding of the pathogenesis of autosomal dominant polycystic kidney disease have led to the development of potential therapeutic targets and agents (63). A number of drugs are now undergoing investigation in phase II or phase III clinical trials. For example, combined somatostatin and tolvaptan blocks the effect of cyclic adenosine monophosphate and inhibits fluid secretion and cell proliferation. Rapamycin inhibits the mTOR pathway, exerting an antiproliferative effect on renal epithelium. Triptolide, which affects calcium signaling, also exhibits antiproliferative effects. A number of other agents may prove helpful for halting the progression of autosomal dominant polycystic kidney disease (63). Drugs that are targeted at the mTOR pathway may be useful in treating tuberous sclerosis complex and von Hippel-Lindau–associated renal cysts. VEGF antagonists also have an effect on von Hippel-Lindau–associated renal disease but are still undergoing clinical testing to determine their efficacy and identify any side effects. With so much research underway, it seems likely that clinically effective treatments for this fascinating group of renal diseases will be available in the near future.

Summary

Renal cystic diseases in adults encompass a wide spectrum of inherited, developmental, and acquired disorders. Recent advances in cytogenetics and molecular biology have helped identify the genes that are responsible for normal functioning of the primary cilia of renal tubular epithelial cells and have shown that hereditary...
renal cystic diseases are caused by defects in the structure and functioning of the renal cilia. These genes and the proteins they produce have been extensively studied and characterized: PKD1 and PKD2 play an important role in renal epithelial development and homeostasis by regulating intracellular calcium transport; TSC2 and TSC1, the genes implicated in the pathogenesis of tuberous sclerosis, and the tumor suppressor gene that prevents von Hippel-Lindau disease, are responsible for maintaining normal renal ciliary structure and function. More detailed knowledge of the molecular mechanisms that underlie the development of renal cystic diseases has led to the development of new therapeutic agents that are now undergoing clinical trials. Cross-sectional imaging not only aids in the identification of renal cystic diseases but permits the monitoring of disease progression and treatment response.

References

In addition to polycystin-1 and polycystin-2, many other proteins (eg, nephrocystin, fibrocystin, polaris, Bardet-Biedl syndrome, and oral-facial-digital syndrome proteins) are localized to the surface of the cilium (4). Abnormality of these proteins, with resultant ciliary dysfunction, is a universal characteristic of inherited renal cystic diseases, which are discussed in the next section.

MR imaging–based renal and cyst volumetry allows the assessment of renal and cyst volumes, which may be used as indicators of disease progression or treatment response (11).

At imaging, multiple renal cysts intermingled with angiomyolipomas in both kidneys are characteristic features of tuberous sclerosis complex (Fig 7) (9,34).

At US, small echogenic kidneys with multiple renal cysts are seen bilaterally. At CT and MR imaging, markedly atrophic kidneys with multiple cysts of varying sizes are identified (Fig 9).

At cross-sectional imaging, localized renal cystic disease may appear as a conglomerate mass of multiple simple cysts of various sizes, separated by enhancing or atrophic renal tissue, without a definite capsule (Fig 15) (60,61).