

ABSITE CORNER

Polycystic kidney disease

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SUMMARY & GENERAL INFORMATION

Key points: (a) Polycystic kidney disease (PKD) is one of the most common genetic disorders; (b) There are two main types of PKD – autosomal dominant (most common) and autosomal recessive; (c) Diagnosis of PKD relies on a combination of clinical history, family history, imaging studies (computed tomography, ultrasound) and clinical findings (hematuria, hypertension, proteinuria); (d) Extrarenal manifestations of PKD include hepatic cysts, pancreatic and intestinal cysts, colonic diverticula, inguinal and abdominal wall hernias, valvular heart disorders, and cerebral aneurysms; (e) Treatment is centered on ameliorating symptoms and providing supportive care – therapy consists of adequate analgesia for pain symptoms, antibiotics for urinary tract infections, antihypertensive medications, renal supportive therapy; (f) Surgical indications include surgical decompression of large cysts and renal transplantation for end-stage renal failure.

ABSITE CORNER is a section of OPUS 12 Scientist dedicated to brief topic reviews geared toward resident preparation for the American Board of Surgery In-Training Examination. Each bi-monthly edition of OPUS 12 Scientist will contain one or two condensed overviews, accompanied by a list of selected references. Resident contributions via regular article submission process are welcome, subject to Editorial Board and Section Editor approval.

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POLYCYSTIC KIDNEY DISEASE

Polycystic kidney disease (alternatively, polycystic kidney syndrome) is a progressive, genetic disorder that primarily affects the kidneys. While it is characterized mainly by the presence of multiple renal cysts, this disease process can also affect the liver, pancreas, heart and brain.

Polycystic kidney disease is one of the most common genetic disorders. There are two main types of polycystic kidney disease (PKD), each characterized by a different inheritance pattern. The autosomal dominant (adPKD) form affects approximately 1 in 400 to 1000 live births, while the autosomal recessive (arPKD) type occurs in approximately 1 in 10,000 to 20,000 live births.

PATHOPHYSIOLOGY OF PKD

There are three basic pathophysiologic processes involved in PKD with regard to formation of renal cysts and their progressive enlargement. These processes can be summarized as follows: (a)

tubular cell hyperplasia – likely mediated by factors that control cell proliferation, dysregulation of apoptosis, or the balance between these processes; (b) **tubular fluid secretion** – changes initiated by processes related to tubular cell hyperplasia that lead to formation of fluid-filled cysts via secretion of fluid by tubular cells and concurrent efferent tubular obstruction or slow/absent flow; (c) **abnormalities in tubular extracellular matrix and/or function** – thought to be responsible for amplifying tubular cell hyperplasia and tubular fluid secretion. Of interest, 70% of patients with adPKD have defective afferent or efferent tubular connections.

In over 85% of cases, adPKD is the result of mutations in the PKD1 gene (chromosome 16). This gene codes for the protein polycystin 1. Most other cases are caused by mutations in the PKD2 gene on chromosome 4, which codes for polycystin 2. A few familial cases of adPKD have been found to be unrelated to either locus. Polycystin 1 is thought to regulate tubular epithelial cell adhesion and differentiation while polycystin 2 is believed to function as an ion channel, with mutations causing fluid secretion into cysts. Mutations in these proteins may alter the function of renal cilia, which enable tubular cells to sense flow rates. It is hypothesized that tubular cell proliferation and differentiation are linked to flow rates and that ciliary dysfunction may thus lead to cystic transformation.

Early in the disease, tubules dilate and slowly fill with glomerular filtrate. Eventually, the tubules separate from the functioning nephron and fill with secreted rather than filtered fluid, forming cysts (**Figure 1**). Hemorrhage into cysts may occur, resulting in hematuria. Patients are also at higher risk for acute pyelonephritis and urinary calculi (20%). Vascular sclerosis and interstitial fibrosis eventually develop and typically affect less than 10% of tubules. Nevertheless, renal failure develops in about 35 to 45% of patients by age 60. Interstitial inflammation and fibrosis are responsible for disease progression in all forms of PKD.

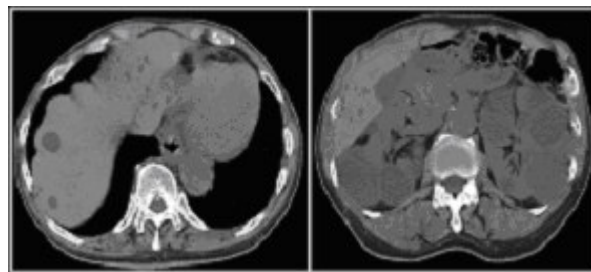


Figure 1. Computed tomographic appearance of multiple hepatic and renal cysts in a patient with adPKD.

AUTOSOMAL DOMINANT PKD

Autosomal dominant PKD is the most common form of PKD, and usually develops later in life. It is characterized by progressive cyst development and associated bilateral renal enlargement. This form of disease is less severe and often produces no symptoms, with only approximately 50% of cases diagnosed during the patient's lifetime.

Autosomal dominant PKD is associated with mutations in the gene PKD1 in 85% of cases (chromosome 16). In approximately 15% of patients, mutations in the gene PKD2 are causative (chromosome 4). Another locus, PKD3, is associated with the disease in a small fraction of cases. In approximately 25% to 40% of patients, PKD occurs without any family history of the disease.

Renal manifestations of this disorder include renal insufficiency/failure, hypertension, and pain. Approximately 50% of patients with adPKD develop end-stage renal disease by age 60. In addition, this form of PKD also tends to be associated with cystic lesions in the liver (which may eventually lead to hepatic cirrhosis), seminal vesicles, pancreas, and arachnoid mater. Other, non-cystic abnormalities include intracranial aneurysms and dolichoectasis, dilatation of the aortic root, dissection of the thoracic aorta, mitral valve prolapse, and abdominal wall hernias.

Clinical manifestations of adPKD include hypertension, fatigue, and mild to severe back/flank pain. Urinary tract infections (UTIs) may also be seen. Patients with advanced-stage PKD may develop end-stage renal failure and requirement for dialysis. Of interest, cysts and renal failure occur at an earlier age in patients with PKD1 (approximately 55-60 years), as compared to non-PKD1 patients (approximately 70 years).

AUTOSOMAL RECESSIVE PKD

Autosomal recessive PKD (arPKD) is seen less commonly than the autosomal dominant form. The arPKD is often lethal, with signs and symptoms usually apparent at birth or during early infancy. It is associated with mutations in the PKDHD1 gene (6p12.2 chromosomal locus). Fibrocystin/polyductin, a protein encoded by PKDHD1, is expressed on the cilia of renal and bile duct epithelial cells and is thought to be crucial in maintaining the normal tubular/ductal architecture. However, the precise function of this protein has yet to be completely studied or understood. One theory states that the primary defect in arPKD is linked to ciliary dysfunction. The arPKD is characterized by nonobstructive, bilateral, symmetric dilatation and elongation of 10-90% of the renal collecting ducts, accounting for a wide variability in renal dysfunction.

CLINICAL MANIFESTATIONS

Autosomal dominant PKD usually causes no symptoms initially. One half of patients remain asymptomatic, never develop renal insufficiency or failure, and are never diagnosed. Most patients who develop symptoms do so by the end of the second decade of life. Common complaints include low-grade flank, abdominal, and/or lower back pain due to cystic enlargement of the kidneys and symptoms of infection. Acute pain is usually due to hemorrhage into cysts or passage of a renal calculus. Fever is seen commonly with acute pyelonephritis.

Signs are nonspecific and include hematuria (64%), hypertension (50%), and proteinuria (20%). Anemia is less common than in

other types of chronic renal failure, presumably because erythropoietin production is preserved. In advanced disease, the kidneys may become grossly enlarged and palpable, causing fullness in the upper abdomen and flank.

PKD: EXTRARENAL MANIFESTATIONS

Extrarenal manifestations are common. About one third of patients have hepatic cysts, which typically do not affect liver function but may cause right upper quadrant pain if they enlarge or become infected. Patients also have a higher incidence of pancreatic and intestinal cysts, colonic diverticula, and inguinal and abdominal wall hernias.

Valvular heart disorders (most often mitral valve prolapse and aortic regurgitation) can be detected by cardiac ultrasonography in 25% to 30% of patients. Aortic regurgitation results from aortic root dilation due to arterial wall changes (including aortic aneurysm). Other valvular disorders may be due to collagen abnormalities. Valvular disorders rarely cause symptoms but occasionally may require valvular replacement. Coronary artery aneurysms also have been reported.

About 4% of young adults and up to 10% of elderly patients with PKD have cerebral aneurysms (**Figure 2**). Aneurysms rupture in 65% to 75% of patients, usually before age 50. Risk factors include family history of aneurysm and/or rupture, larger aneurysms, and poorly controlled hypertension. Symptoms and signs of unruptured cerebral aneurysm include headache, nausea and vomiting, and cranial nerve deficits – if present, these warrant immediate intervention.

DIAGNOSIS OF PKD

Diagnosis of PKD is made by clinical history, family history, physical examination, and imaging. Ultrasonography or computed tomography (CT) are the imaging tests of choice, usually showing extensive cystic changes throughout the kidneys (**Figure 1**) and a moth-eaten appearance due to cysts that displace functional tissue. Urinalysis detects mild proteinuria and microscopic or macroscopic hematuria. Gross hematuria may be due to a dislodged calculus or to hemorrhage from a ruptured cyst. Pyuria is common even without bacterial infection. Initially, BUN and creatinine are normal or only mildly elevated, but they slowly increase, especially when hypertension is present. Rarely, polycythemia may be present.

Patients with symptoms of cerebral aneurysm require high-resolution CT or magnetic resonance angiography. There is no uniform agreement on whether asymptomatic patients should be screened for cerebral aneurysms, at what age, and how often. A reasonable approach is to screen patients with adPKD and a family history of hemorrhagic stroke or cerebral aneurysm.

Genetic testing for PKD mutations is currently reserved for patients with PKD and no known family history. Genetic counseling is recommended for first-degree relatives of patients with adPKD.

PKD: PROGNOSTIC CONSIDERATIONS

By age 75 years, 50% to 75% of patients with adPKD require renal replacement therapy (dialysis or transplantation). Predictors of more rapid progression to renal failure include earlier age at diagnosis, male sex, black race, PKD1 genotype, larger renal

volume, gross hematuria, rapid increase in kidney size, hypertension, hepatic cysts (in women), and UTIs (in men). Autosomal dominant PKD does not increase risk of renal cancer, but if patients with adPKD develop renal cancer, it is more likely to be bilateral. Without dialysis or transplantation, patients usually die of uremia or complications of hypertension. About 10% die of intracranial hemorrhage from a ruptured cerebral aneurysm. With dialysis or transplantation, patients die of valvular cardiomyopathy, disseminated infection, or ruptured cerebral aneurysm.

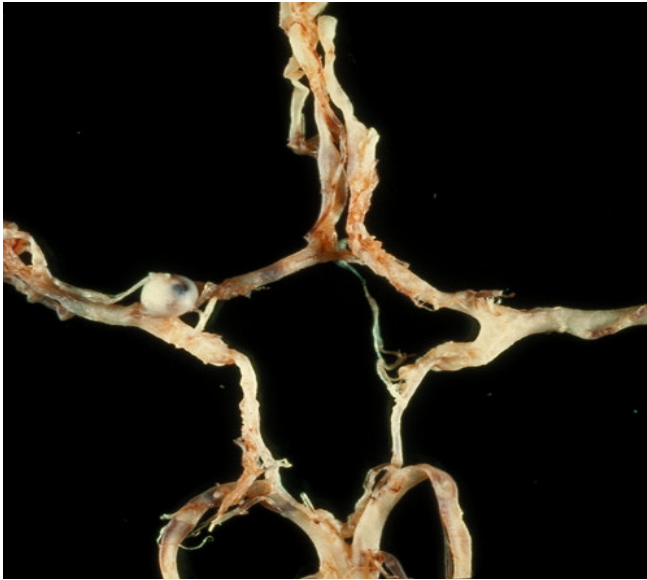


Figure 2. Example of a cerebral aneurysm seen in association with polycystic kidney disease.

TREATMENT OF PKD

There is no cure available for PKD. Treatment is centered on ameliorating symptoms and providing supportive therapy (such as renal replacement therapy).

For mild pain symptoms, over-the-counter medications may be effective. Percutaneous aspiration of cysts may help manage severe pain due to hemorrhage or compression but has no effect on long-term outcome. For severe refractory pain, surgical decompression of large cysts may provide effective symptomatic relief. Both open and laparoscopic surgical approaches have been described. However, surgery does not slow the progression of the chronic renal failure.

For urinary tract infections, antibiotics remain the mainstay of therapy. Early treatment is important because infection can secondarily involve the cysts. Cyst infections are difficult to treat due to poor antibiotic cyst penetration. Nephrectomy is an option to relieve severe symptoms due to recurrent infections.

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Strict control of hypertension is very important in PKD. Adequate blood pressure control may slow the progression of PKD. In untreated PKD, sequelae of hypertension may contribute to patient mortality. In addition, protein intake should be restricted to 0.6 to 0.7 gm/kg/day.

End-stage renal disease associated with PKD is amenable to two forms of treatment – dialysis and transplantation. Hemodialysis, peritoneal dialysis, or renal transplantation can be utilized in this patient population. While on dialysis, patients with adPKD maintain higher hemoglobin levels than any other group of patients with end-stage renal failure. Kidneys from non-PKD donors transplanted into patients with PKD do not develop cysts. Risks associated with renal transplantation include a variety of surgical complications as well as problems associated with chronic immunosuppression.

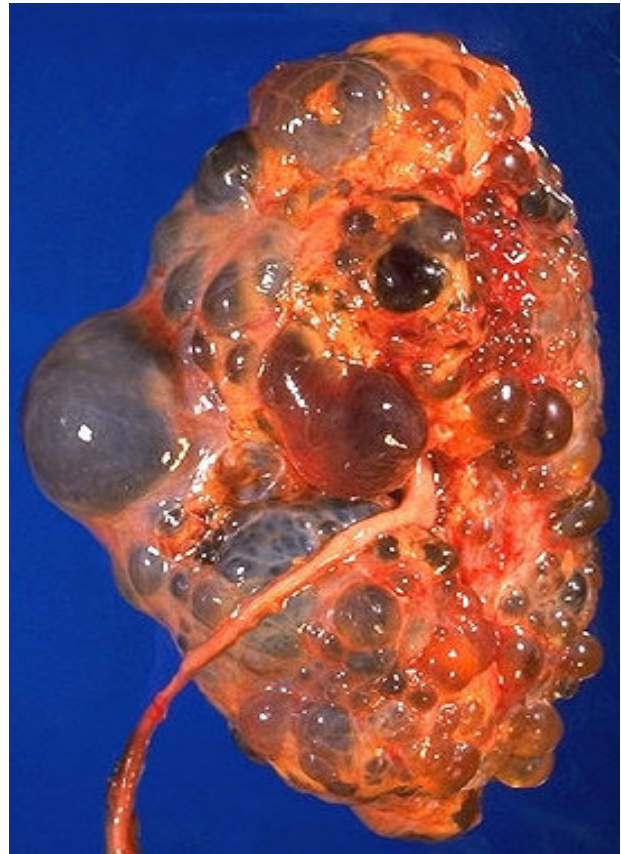


Figure 3. Pathology specimen demonstrating cystic changes in advanced polycystic kidney disease.

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