

Autosomal Dominant Polycystic Kidney Disease: Etiology, Diagnosis, Renal And Extrarenal Complications

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the third most common systemic hereditary disease. Only hypercholesterolemia and dominant otosclerosis affect a larger population of patients. Its prevalence is estimated to be between 1 in 400 and 1 in 1000. ADPKD accounts for 10% to 15% of end-stage renal disease cases requiring dialysis. The severity of ADPKD is variable and ranges from asymptomatic to renal failure. This variability in expression and disease is evidence that this disease has multiple interrelated genetic components. Over 50% of the patients never progress to ESRD or transplantation. Further, the sequelae of ADPKD are not limited to the kidney. We discuss a case presenting with subarachnoid hemorrhage and also the most common clinical manifestations of ADPKD and their diagnosis and treatment, with specific attention given to intracranial aneurysms in ADPKD.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the third most common systemic hereditary disease. Only hypercholesterolemia and dominant otosclerosis affect a larger population of patients.¹ Its prevalence is estimated to be between 1 in 400 and 1 in 1000.¹ ADPKD accounts for 10% to 15% of end-stage renal disease cases requiring dialysis.^{1,2} The severity of ADPKD is variable and ranges from asymptomatic to renal failure. This variability in expression and disease is evidence that this disease has multiple interrelated genetic components. Over 50% of the patients never progress to ESRD or transplantation.^{2,3} Further, the sequelae of ADPKD are not limited to the kidney. The following case report and discussion is a brief introduction to the most common clinical manifestations of ADPKD and their diagnosis and treatment, with specific attention given to intracranial aneurysms in ADPKD.

CASE REPORT

A 61 year old white male who found unconscious outside his place of work. After quickly regaining consciousness, he was confused and complained of "the worst headache of his life" and severe nausea. During transport to the hospital, the patient experienced cardiac and respiratory arrest. His Glasgow Coma Scale (GCS) on arrival to the emergency department was 11T (E4, M6, V1). Head CT examination revealed subarachnoid blood in the suprasellar and

perimesencephalic cisterns, and bilateral sylvian fissures. There was no evidence of intraventricular hemorrhage, midline shift, herniation or cerebral infarcts. Abdominal CT revealed multiple bilateral kidney cysts, the largest of which measured 8 x 8 x 6.5 cm. There was no evidence of hydronephrosis or nephrolithiasis. The liver had three cysts with the largest measuring 2.2 cm. The patient's past medical history was significant for recurrent sinusitis. Angiography revealed a partially thrombosed anterior communicating artery aneurysm which was surgically clipped. A nephrology consult was obtained due to the suspicion of undiagnosed ADPKD. The patient had a single episode of gross hematuria 5 years prior to admission, no history of urinary tract infection, nephrolithiasis, flank pain, or hypertension and no family history suggestive of kidney disease. Based on his medical history and radiologic findings, the patient was diagnosed with ADPKD. The patient's clinical course was complicated by recurrent ventriculostomy-dependent hydrocephalus, sinusitis, aspiration pneumonia, respiratory failure requiring tracheostomy, cerebral vasospasm, symptomatic anemia, adynamic ileus requiring parenteral nutritional support, meningitis, deep venous thrombosis with Greenfield filter placement, and Terson's syndrome. On discharge from the hospital, the patient's only neurologic deficit was severe vision loss secondary to Terson's syndrome, mild right lower extremity weakness, and debilitation.

RENAL CYSTS

When a patient is found to have multiple kidney cysts the differential diagnosis includes simple idiopathic cysts, acquired cyclic kidney disease (ACKD), autosomal recessive polycystic kidney (ARPKD), medullary sponge kidney (MSK) and medullary cystic kidney (MCK), unilateral renal cystic disease (URCD), and autosomal dominated polycystic kidney disease (ADPKD). Below, a brief review of the most common causes of renal cystic disease is followed by a discussion of the genetics, diagnostic features and clinical manifestations of autosomal polycystic kidney disease.

DIFFERENTIAL DIAGNOSIS OF RENAL CYSTS

Renal cyst formation increases with age. By the time an individual reaches fifty years of age, they have a 50% chance of developing a renal cyst.⁴ The majority of simple idiopathic cysts are found coincidentally while the patient is undergoing radiographic imaging for a different problem. These cysts are generally asymptomatic, are usually located on the outer portion of the kidney cortex, and contain clear fluid that has the composition of plasma ultrafiltrate. In most instances computed tomography (CT) and ultrasonography are used once a cyst has been discovered to differentiate between benign and malignant renal masses.

Acquired polycystic disease occurs in end stage renal disease (ESRD) patients undergoing dialysis. The incidence of multiple cyst formation increases with the length of time on dialysis. After three years of dialysis, 50% of patients will show evidence of multiple cyst formation.⁵ Both peritoneal and hemodialysis are associated with the cyst formation. The kidney in ESRD is small and diagnosis is made with ultrasonography followed by CT scanning with contrast.

Autosomal recessive polycystic kidney disease (ARPKD) is characterized by multiple small cysts at the corticomedullary junction. Death usually occurs secondary to renal failure and within the first year of life. ARPKD is also associated with congenital hepatic fibrosis. The incidence of ARPKD is 1 per 10,000 to 40,000 live births, the disease is usually discovered neonatally or perinatally.⁶ About 60% of affected children die within the first month of life, and in those that live past one month the mean survival is approximately 6 years.⁶ Hypertension, edema, impaired liver and kidney function, and frequent urinary tract infections (UTI) are prevalent in ARPKD. Children with ARPKD are at risk for hepatic fibrotic disease and are treated with dialysis and renal transplantation when ESRD occurs.⁷

Medullary kidney disorders consist of two distinct diseases, medullary sponge kidney and medullary cystic kidney. Medullary cystic disease is rare, autosomally recessive and has been associated with retinitis pigmentosa.⁴ The two earliest indicators of disease are prolonged childhood enuresis and anemia. ESRD usually occurs in adolescence or early childhood. Medullary sponge kidney (MSK) is more common and is usually diagnosed incidentally. Approximately 10% of patients with nephrolithiasis are found to have MSK and about 50% of patients with MSK develop renal canaculi.⁴ Definitive diagnosis is by intravenous pyelogram (IVP). MSK does not generally result in kidney failure.

Unilateral renal cystic disease (URCD) is a rare disorder characterized by multiple renal cysts that are confined to one kidney. The radiologic, morphologic and histologic appearance of URCD is indistinguishable from ADPKD except that URCD is confined to one kidney while bilateral disease occurs with the latter.⁸ URCD does not have a genetic origin and patients do not progress to renal failure. Like ADPKD, patients suffer from hypertension, flank and abdominal pain, and hematuria.⁸

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

GENETICS

Three distinct gene defects have now been implicated in the pathogenesis of ADPKD and have been designated PKD1, PKD2, PKD3. In 1985, Reeders et al. identified a defect on chromosome 16 (PKD1) that is responsible for 85% of the cases of ADPKD.⁹ PKD2 is located on chromosome 4 and accounts for 10% to 15% of patients with ADPKD.¹⁰ A third gene is involved but its exact location has yet to be mapped.¹²

There is a correlation between symptom severity, age of symptom onset, and the gene location involved. PKD2 patients have a less severe form of ADPKD with a later age of onset and a reduced likelihood of progression of the disease to dialysis or transplantation. The mean age of presentation of symptoms in patients identified with PKD1 is 44.8 years versus 69.1 years in patients with PKD2.¹² The mean age at death or onset of ESRD is 53.0 to 56.7 years in PDK1 and 69.1 to 69.45 years in PKD2.^{12,13} Patients with PDK2 are free of symptoms 75% of the time and only 7.5% progress to ESRD.¹⁴ However, the difference in gene defect location does not completely account for the variability seen

in ADPKD. Variations in severity is also seen within the same family where presumably one would expect similar disease outcomes.¹⁵

Children of families affected with ADPKD have a 50% chance of inheriting the disease. Caregivers should advise their patients about the availability of prenatal screening and the importance of screening asymptomatic relatives. When counseling patients about screening, it is necessary to inform them of the possible negative repercussions of a positive finding of a gene defect with respect to their potential insurability and employment.^{3,16}

DIAGNOSIS

The initial clinical work-up for a patient with suspected ADPKD or for screening a patient with a family history of ADPKD consists of an abdominal ultrasound. One diagnostic criteria commonly used for patients with a family history of ADPKD is the ultrasonographic demonstration of three or more cysts with at least one cyst in each kidney; was developed by Bear and colleagues.¹⁶ Problems with this criteria occur because patients younger than thirty years of age are unlikely to have idiopathic cysts but as one ages the incidence of idiopathic renal cysts increases. By the age of fifty the probability of idiopathic cyst formation increases to 50%.⁴ In addition early in the disease cysts may be too small to be demonstrated increasing the chance of a false negative diagnosis. The likelihood that a patient has ADPKD is diminished if by the age of 60 they have not yet developed multiple kidney cysts.

Ravine et al. has modified the criteria to account for these differences in occurrence of sporadic cysts at different ages in patients with PKD1.¹⁸ They propose diagnosis of ADPKD if there is a positive family history, two renal cysts either unilateral or bilateral in patients under the age of thirty. In patients between the ages of 30 and 59, a minimum of two cysts must be present in each kidney. In patients over the age of 60, four cysts in each kidney is necessary for diagnosis.¹⁸ The use of these criteria reduces the false negative rate of diagnosis to less than 5%.

Demetriou et al. compared genetic testing with ultrasonographic results in patients with PKD2.¹⁴ They found that ultrasound was 100% reliable in ruling out disease in patients at risk genetically over 30 years of age and 96% accurate in diagnosing disease.¹⁴

RENAL CYST FORMATION

Renal disease is the hallmark of ADPKD. Studies have shown that only 2-5% of nephrons are directly affect by cyst formation despite the fact that ADPKD is commonly associated with impaired renal function.² In the earliest stages of development, cysts are contiguous from either the afferent or efferent tubule segments from which they arose. As cysts develop and exceed 2 cm in diameter, approximately 70% will become isolated from their tubular sources of urine, becoming autonomous sacs within the kidney that derive intracavity fluid through cyclic AMP mediated transepithelial fluid secretion.¹⁹ This isolation of the cyst from the urine has important implications when treating urinary tract infections in patients with ADPKD. Cysts vary in size and can be microscopic or as large as 10 cm and may contain several hundred milliliters of fluid.⁷ Cyst growth results in renal parenchymal compression, compromise of adjacent renal parenchyma, atrophy of adjacent tubules, thickening of basement membranes, interstitial inflammation, and ultimately interstitial fibrosis.^{7,19,20}

HEMATURIA

Gross hematuria is often the first presenting sign of ADPKD and the reason patients first seek attention. Gross hematuria is usually secondary to renal cyst rupture into the renal pelvis. Infection, segmental renal infarction, and passage of renal calculi also cause gross hematuria in ADPKD patients.¹⁹ If hematuria is recurrent or persists for more than two weeks and the patient has other risk factors associated with the development of renal malignancies, then the possibility of neoplasm should be investigated.²¹ Renal malignancies do not occur in a greater frequency in ADPKD patients than they do in the general population.²² Treatment of hematuria secondary to cyst rupture consists of rest, hydration and analgesics.

RENAL INFECTION

Infection is a common complication seen in patients with ADPKD. It is more common in females than males. Both urinary tract infection (cystitis and/or pyelonephritis) and renal cyst infections can occur independently or in combination. A negative urine culture cannot exclude renal cyst infection since the lumen of the cyst is not contiguous with the nephron and collecting system of the kidney. Therefore a high degree of suspicion for renal cyst infection should occur in any patient with ADPKD, flank pain, costovertebral tenderness, fever, and sterile urine cultures.⁷

Aminoglycosides are polar drugs and consequently are not transported easily across the renal cyst epithelium and should therefore be avoided in patients with ADPKD when renal cyst infection is suspected.⁷ Trimethoprim-sulfamethoxazole and the fluoroquinolones (ciprofloxacin) are more lipophilic, reaching both inhibitory and bacteriocidal titers of at least 1:32 in cyst fluid.^{23,24} CT guided biopsy of cyst aspirate may be necessary for definitive diagnosis in patients who remain febrile despite appropriate empiric antibiotic therapy to drain abscesses, identify the organism involved, and to test for antibiotic sensitivity.²¹ Since instrumentation of the urinary tract predisposes patients to infections avoidance of instrumentation is recommended.

HYPERTENSION

Mild to moderate hypertension is a common abnormality found in ADPKD patients.²⁵ Patients with mild renal cyst formation are more likely to be normotensive than patients with extensive renal cyst involvement. Renal function in hypertensive ADPKD patients declines faster than normotensive ADPKD patients. Hypertension occurs in over 50% of ADPKD patients.²⁶ The incidence in males has been reported to be 42-66% while 41-61% of female ADPKD patients are hypertensive.^{27,28} Patients with PDK1 are four times more likely to suffer from hypertension than patients with PKD2.¹³ Increased renovascular resistance and ischemia secondary to renal cyst compression is believed to be one of the mechanisms for hypertension development.^{1,29} The renin-angiotensin-aldosterone axis is stimulated in patients with ADPKD as compared with essential hypertensive controls.³⁰ Treatment with the ACE inhibitors benazepril or enalapril or the calcium channel blocker amlodipine have not been shown to affect the progression of renal insufficiency in ADPKD patients.^{25,29} It is unknown if early prolonged treatment of hypertension with these agents before the onset of renal insufficiency will result in a decline in ESRD. Despite these results ACE inhibitors, beta blockers, and calcium channel blockers are all considered first line therapy modalities for hypertensive patients.^{25,29}

RENAL STONES

Nephrolithiasis occurs in 20% to 25% of all ADPKD patients.^{1,31} The exact frequency is variable with some studies reporting a prevalence of only eight percent while others have found the incidence of nephrolithiasis to be as high as thirty-six percent.³¹ The most common stone composition is uric acid and calcium oxalate.³¹ The

diagnosis of renal canaculi is complicated by the distortion of the normal renal anatomy in ADPKD patients and the presence of parenchymal and cyst wall calcifications.³¹ CT scanning with contrast, with its ability to visualize both small and radiolucent stones, is the diagnostic tool of choice. Treatment of ADPKD patients with canaculi does not differ from the treatment of renal stones in the general population.³¹ Urine alkalinization and hydration, percutaneous nephrolithotomy, and extracorporeal shock wave lithotripsy are frequently used treatment modalities.

ABDOMINAL PAIN

Abdominal pain occurs in the majority of ADPKD patients and abdominal pain is the most common complaint in symptomatic patients. It is thought to be secondary to both the size and number of renal cysts. Stretching of the renal capsule and/or traction on the renal pedicle secondary to increased renal weight is believed to be the etiology of abdominal pain.²¹ When pain is present it is necessary to differentiate between cystic pain, pain secondary to cyst infection, renal canaculi, and hemorrhage into the cyst(s). Pain from hemorrhage is usually acute and self-limited. Pain associated with infection is diagnosed by history, urine and serum analysis, and radiologic techniques are used to identify renal canaculi. Management of abdominal pain secondary to renal cysts is conservative with non-narcotic analgesics the preferred initial treatment. Nonsteroid anti-inflammatories and combination analgesics should be avoided due to their potential nephrotoxicity potential.³² If nonsteroidal anti-inflammatory medications are necessary, renal function should be monitored.^{1,21}

Three surgical techniques have been used to relieve the pain associated with ADPKD: needle aspiration and cyst unroofing either by an open abdominal or laparoscopic procedure. The criteria for surgical intervention is failure of conservative management, as defined by one of the following: chronic pain that interferes with activities of daily living or decreases the quality of life, disability, and/or narcotic dependence.²¹ Cyst decompression by needle aspiration initially reduces pain but the effect is short-lived, lasting only 3 to 6 months.³² This temporary effect is believed to be due to the re-accumulation of fluid in needle aspirated cysts. Open reduction surgery allows for more extensive cyst decompression and results in pain-free relief in 80% of patients at 12 months with 62% of patients remaining pain-free at 24 months.³² There is only limited experience with the use of laparoscopic techniques in

ADPKD cyst decompression and initial studies that utilized a limited number of patients have to date proved disappointing. While the length of hospital stay and post-operative convalescence is less with laparoscopic surgery, fewer cysts can be decompressed in one surgical procedure and many cysts are inaccessible.³² Hypertension is associated with large and/or extensive renal cyst development and is usually improved after cyst reduction surgery, though the benefit is usually transitory. Only approximately 22% of patients remain normotensive three months after surgery.³² Cyst decompression surgery does not have a deleterious affect on renal function but it also does not slow the progression of ADPKD associated renal failure.

END STAGE RENAL DISEASE

ADPKD is associated with end stage renal disease (ESRD) though the progression to ESRD is highly variable. The disease causes renal failure in 25% of patients by the age of 50 and in 50% of patients by the age of 70.⁴ As mentioned previously, the genotype of ADPK is related to the severity and progression of renal disease. Patients with PKD1 have renal symptoms earlier and progress to kidney failure at a mean age of 54.3 to 56.7 years while patients with PKD2 manifest renal failure at a mean age of 69.4 to 74.0 years.^{12,13} Diagnosis at a young age, male gender, hypertension, cardiovascular disease, hepatic cysts, three or more pregnancies and recurrent urinary tract infections have all been implicated as prognostic signs associated with the development of ESRD.^{33,34}

HEPATIC CYSTS

The most common extrarenal manifestation of ADPKD is hepatic cysts. They rarely occur in childhood or adolescence but their incidence increases in the second through fifth decades of life and by 50 years of age 80% of patients with ADPKD have hepatic cysts.³⁴ Females are more likely to form hepatic cysts and their development is believed to be related to female sex hormones and pregnancy. Women with the greatest number of hepatic cysts had more pregnancies and their cysts were larger and more numerous when compared to women who were never pregnant. ³⁴ The number and size of hepatic cysts was also correlated with the severity of renal disease and increasing age.³⁴ Unlike renal cysts, hepatic cysts do not usually affect liver functioning. Complications related to liver cysts include infection, carcinoma and hemorrhage, with infection being the most common.³⁴ Fever, pain over the liver, abnormal liver

function tests and increased bilirubin are indications of hepatic cyst infection. Since hepatic cysts rarely increase liver function tests, any increase is highly suspicious of hepatic cyst infection.³⁴ Treatment with antibiotics and needle aspiration for cyst drainage is usually sufficient, surgical resection is rarely indicated.³⁴

DIVERTICULAR DISEASE

Patients with ADPKD have an increased incidence of diverticular disease once ESRD occurs. One study found that incidence of colon diverticula in patients with both ESRD and ADPKD to be 83% and one fourth of the patients developed colonic perforation with abscess formation. ³⁶ End stage renal disease patients without ADPKD had a colonic diverticula incidence of 32%. ³⁶ The diagnosis of diverticulitis and colon perforations is difficult because abdominal pain and fever, the most commonly occurring symptoms of diverticular disease are also indicative of renal and liver cyst infection, hemorrhage and rupture.³⁷ Prior to the development of ESRD there is no increase in diverticular disease.³⁵

INTRACRANIAL ANEURYSMS AND OTHER VASCULAR COMPLICATIONS

There is an increased risk for both symptomatic and asymptomatic intracranial aneurysms (ICA) in patients with both PDK1 and PKD2.^{38,39,40} Patients with ADPKD experience ICA rupture at an earlier age and have an increased mortality and morbidity than ICA rupture in the general population.^{41,42} There is great variability in the literature prevalence data for ICA in ADPKD patients. Rates from 0-41% have been reported. (Reviewed in references 16 and ⁴³) It is difficult to access the true incidence of ICA's from these studies since they used different patient populations, various sample sizes, included both prospective and retrospective studies, and used multiple radiologic techniques with different sensitivities and specificities. Two prospective studies utilizing magnetic resonance angiography (MRA) in ADPKD patients estimated the prevalence of ICA at 11.0% to 11.7% with a 22% prevalence in patients with a family history of aneurysms.^{44,45}

Any patient with a focal neurologic change, sudden loss of consciousness or new onset severe headache should be screened for an aneurysm. Both high resolution computerized tomography (CT) with or without angiography and MRA has been used. Some have suggested that MRA should be the screening method of choice because it does not

involve the use of intravascular contrast material that may be contraindicated in patients with impaired renal function. 45 A transient complication rate with CT angiography of 25% in ADPKD patients has been reported.⁴¹ The complication rate in non-ADPKD patients undergoing screening for symptomatic aneurysms in the same institution was only 10%. There is no consensus in the literature for prophylactic screening of asymptomatic patients for the presence of an ICA. Chapman and colleagues have proposed screening ADPKD patients with aneurysms less than 7 mm every 1 to 2 years, aneurysms 7 to 10 mm yearly, and a five year follow-up in patients with a family history of ICA rupture.⁴¹ Torres and colleagues recommend MRA follow-up of small ICA's (< 9 mm) on a yearly basis initially and a 3-year screening program for patients a history of ICA rupture.⁴⁶

The treatment of choice for subarachnoid hemorrhage in ADPKD patients is microsurgical clipping. Endovascular coiling of the aneurysm is an option depending on the age of the patient and the size and configuration of the aneurysm. Surgery is indicated in asymptomatic found aneurysms of 10 mm or greater.⁴¹ The treatment of asymptomatic aneurysms less than 10 mm is controversial.

Little is known about both the natural history of small asymptomatic aneurysms and the rate of growth and stability of de novo aneurysms in patients with a previous history of aneurysm rupture in ADPKD patients. Weiber and his colleagues in the International Study Of Unruptured Intracranial Aneurysms investigated the natural history of unruptured ICA in the general population in 2621 patients in 53 centers in the United States, Canada and Europe. The study consisted of a retrospective arm which assessed the natural history of unruptured intracranial aneurysms and a prospective arm which assessed the surgical morbidity and mortality of newly diagnosed unruptured aneurysms. Within each study arm two groups were evaluated. Group 1 consisted of patients with no previous history of a SAH and patients in group 2 had a history of a SAH from a different aneurysm. In the retrospective the study, Weiber and colleagues found a cumulative rupture rate of 0.05% per year in aneurysms less than 10 mm in patients without a history of previous SAH (group 1) and a 0.5% yearly rupture rate in patients with a history of SAH from a different aneurysm (group 2).⁴⁷ In the same study aneurysms larger than 10 mm were found to rupture at an annual rate of 1% per year in both patient groups. In addition to size aneurysm location affects the rupture rate. In group 1 aneurysms in the tip of

the basilar artery, vertebrobasilar, posterior cerebral artery, and posterior communicating artery were more likely to rupture while in group 2 only basilar-tip artery aneurysms were more likely to rupture. The surgical morbidity and mortality in the prospective arm of the study was 17.5% at 30 days and 15.7% at one year in group 1, and 13.6% at 30 days and 13.1% at one year in group 2. The relevance of this study to ICA's in ADPKD patients is unknown. The decision to treat or watch an asymptomatic aneurysm is complicated by the fact that surgical treatment of unruptured aneurysms has a lower mortality and morbidity rate and is technically easier than the surgical treatment after rupture.⁴⁰ The decision to operate on a small unruptured aneurysm is best made in consultation with a neurosurgeon taking into account the risk of rupture per year and the morbidity and mortality of surgery on both ruptured and unruptured aneurysms.

Other vascular complications have been associated with ADPKD. There are reports of increases in aortic, thoracic, coronary and vertebral dissecting aneurysms. The incidence of these vascular diseases is rare which makes data on their occurrence difficult to obtain. Abnormalities of cardiac valves have been reported, one study found a 26% prevalence of mitral valve prolapse, a 8% prevalence of aortic incompetence and a 15% incidence of tricuspid incompetence.⁴⁸ The natural history of the valvular disorders does not differ between patients with ADPKD and those who have idiopathic cardiac valvular disease. Treatment of valvular dysfunction is the same in ADPKD patients and the general population.⁴¹

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