Images in Hypertension

L. Michael Prisant, MD, Section Editor

Polycystic Kidney Disease

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Polycystic kidney disease, an inherited systemic disorder, is characterized by the development of multiple cysts in the kidneys and other organs. Patients can present at any age, but more often come to clinical attention (unless there is a family history) after age 30. Patients who are diagnosed before age 30 have a worse renal survival. Although palpation of the abdomen occasionally provides a clue to the presence of polycystic kidney disease, radiographic procedures most often suggest the diagnosis. Mutations in the PKD1 *or* PKD2 *genes give rise to cyst formation. Flank pain, hematuria, polyuria, nephrolithiasis, urinary tract infections, and hypertension may be part of the syndrome of polycystic kidney disease. It is the fourth most common cause of end-stage renal disease. Blood pressure treatment goals are less than 130/80 mm Hg. Treatment should include the use of angiotensin-converting enzyme inhibitors. (J Clin Hypertens. 2005;7:617–619,625)* ©2005 Le Jacq Ltd.

Polycystic kidney disease (PCKD) is an inherited systemic disorder characterized by the development of multiple cysts in the kidneys and progressive renal failure. Extrarenal manifestations include cysts in other organs such as the liver and pancreas, cerebral aneurysms, and mitral valve prolapse. Patients can present at any age, but they often come to clinical attention (unless there is a family history) after age 30. The diagnosis is typically made by age 30 in a patient with a positive family history. Patients who are diagnosed before age 30 have a worse renal survival. Ultrasound, computed tomography scanning, and magnetic resonance imaging (MRI) show numerous cysts in both kidneys. Hypertension is a frequent and early finding in these patients. Similar to chronic kidney disease from other causes, the presence of hypertension is a major determinant of both progression of the disease and mortality from cardiovascular disease.

Figure 1 shows typical features of PCKD seen on ultrasonography. There are multiple cysts in the enlarged right kidney, which measures 16.42 cm in length. Figure 2 displays an MRI of multiple cysts in both kidneys. Polycystic kidney disease is a common inherited disorder with both autosomal dominant and recessive forms. The autosomal dominant form occurs in 1 in 800 live births and accounts for 2%–10% of all end-stage renal disease in North America and Europe.[1,2] Less than 50% of patients are diagnosed clinically. Eighty-five percent of autosomal dominant PCKD occurs because of a mutation in the *PKD1* gene on chromosome 16. The gene product is polycystin-1, a large transmembrane protein with widespread distribution. The other 15% of patients with autosomal dominant PCKD have a mutation in the *PKD2* gene on chromosome 4, which encodes for polycystin-2. Patients with the mutation in polycystin-1 have a more aggressive form of the disease and develop end-stage renal disease by a mean age of 53.[3,4] Both forms have a wide variety of extrarenal manifestations. These include cysts in the liver, pancreas, and choroid plexus, intracerebral aneurysms, aortic aneurysms, valvular heart disease, left ventricular hypertrophy, colonic diverticula, and abdominal wall and inguinal hernias.[5]

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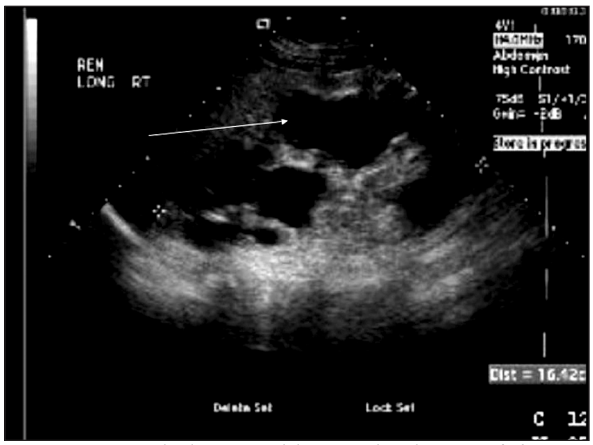

Figure 1. Renal ultrasound longitudinal view of the right kidney of a patient with polycystic kidney disease. The kidney measures 16.42 cm in length and demonstrates multiple cysts and loss of the normal corticomedullary architecture.

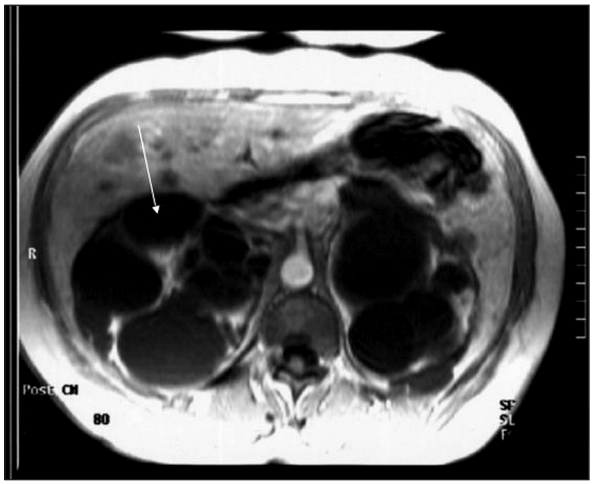

Figure 2. Magnetic resonance imaging showing multiple cysts in both kidneys

There is a striking variability in the clinical manifestations among patients and even within families. Over 200 mutations have been identified for the gene encoding polycystin-1, and there seems to be little correlation between a specific mutation and the phenotype. Polycystin-1 is important in the normal development and regulation of renal tubular epithelium. Cysts arise from these cells, and several different mechanisms of cyst formation have been proposed. Abnormalities in gene expression, cell polarity, fluid secretion, apoptosis, and extracellular matrix deposition have all been described in PCKD.[6] All tubular segments can be affected, but less than 10% of nephrons are involved. Cysts enlarge with age and may participate in parenchymal destruction of the remaining nephron segments through apoptosis. The histologic picture consists of cysts, interstitial fibrosis, tubular atrophy, and advanced sclerosis of preglomerular vessels.[7]

Patients typically present with flank pain, hematuria, renal failure, palpable kidneys, and hypertension. In addition, they are prone to develop concentrating defects with polyuria, urinary tract infections, and nephrolithiasis. Proteinuria is not a characteristic finding in patients with PCKD, and most patients excrete less than 300 mg of protein in 24 hours. Demonstrating large kidneys with multiple cysts bilaterally usually establishes the diagnosis. There can be hundreds of cysts in each kidney, some measuring up to 20 cm in diameter. The diagnostic criteria were modified in 1994 after Ravine and colleagues[8] examined the use of ultrasound and DNA linkage in patients with PCKD-1 and their family members. They determined that patients less than 30 years of age had to have at least two cysts, either unilateral or bilateral, to be diagnosed with PCKD-1. Patients 30–59 years of age required two cysts in each kidney, and patients older than 60 years of age required at least four cysts in each kidney for the diagnosis.

Hypertension is a frequent and early finding in patients with PCKD.[9] It has been reported to occur in up to 75% of patients, depending on the definition employed. Hypertension occurs at an earlier age (mean, 29 years) compared with the usual onset of essential hypertension in the general population and frequently precedes the development of renal failure.[10]

Several mechanisms have been proposed regarding the pathogenesis of hypertension in this disease. Renal structure has been shown to be related to the development of hypertension.[10] Chapman and colleagues[11] used MRI to measure renal and cyst volume in patients with PCKD and normal renal function. They found that higher cyst volume was directly related to the presence of hypertension. As previously mentioned, the histologic findings in PCKD show vascular changes early on, even when renal function remains normal.[7] Investigators have proposed that cyst expansion leads to regional renal ischemia and activation of the renin-angiotensin-aldosterone system. An earlier study by Chapman and colleagues[12] demonstrated increased plasma renin levels in hypertensive patients with PCKD compared with patients with essential hypertension. Cysts have been shown to synthesize renin.[13] Finally, an abnormal pressure–natriuresis response to salt loading has been described and may contribute to the development of hypertension.[14]

Hypertension adversely impacts progression of renal failure in patients with PCKD and contributes to increased cardiovascular risk. Figures 3 and 4 summarize the incidence and point prevalence rates of end-stage renal disease secondary to

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PCKD compared with patients with end-stage renal disease from diabetes and hypertension.[15] Several studies have shown poorer renal survival in hypertensive PCKD patients (blood pressure [BP] >140/90 mm Hg) compared with PCKD normotensive patients.[3,16] Despite these findings, the optimal BP goal and antihypertensive medication have not been determined. The Modification of Diet in Renal Disease (MDRD)[17] study enrolled 200 patients with PCKD. They were randomized to standard mean arterial pressure of 107–113 mm Hg vs. a low mean arterial pressure of 92–98 mm Hg and followed for a mean of 2.2 years. There was no benefit in the preservation of renal function in the low BP group. Similar results were reported by Schrier and colleagues.[18] They followed 75 hypertensive PCKD patients for 7 years after being randomized to rigorous (<120/80 mm Hg) vs. standard (135–140 mm Hg/85–90 mm Hg) BP control. There was no difference in progression of renal disease between the two groups; however, there was a significant decrease in left ventricular hypertrophy with more rigorous BP control. Left ventricular hypertrophy is a major cardiovascular risk factor. Because most patients with PCKD die of cardiovascular complications, this is an important clinical finding.

Finally, a recent meta-analysis examined the effect of angiotensin-converting enzyme (ACE) inhibitors on progression of PCKD.[19] A total of 142 patients in eight studies were randomized to antihypertensive therapy either with or without an ACE inhibitor. After a mean follow-up of 2.3 years, there was no difference in progression of disease. ACE inhibitors were beneficial in decreasing urinary protein excretion in patients with higher baseline proteinuria. Thus, there may be a beneficial effect on cardiovascular risk with lower BP (<120/80 mm Hg) in patients with PCKD, but no evidence of slowing progression of the disease with more rigorous BP control or the use of ACE inhibitors. Until further randomized, controlled trials are conducted in patients with PCKD, a BP goal of less than 130/80 mm Hg, as recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7), should be the target unless there is evidence of cardiovascular disease.[20]

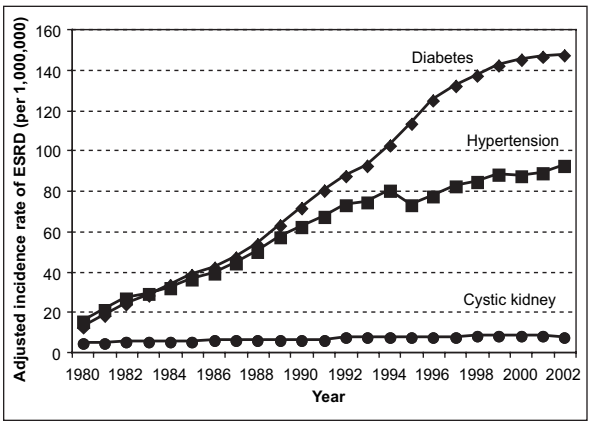

Figure 3. Incidence rates of reported end-stage renal disease, adjusted. The incidence of end-stage renal disease secondary to polycystic kidney disease is compared with end-stage renal disease from diabetes and hypertension. Derived from USRDS 2004 Annual Data Report.[15]

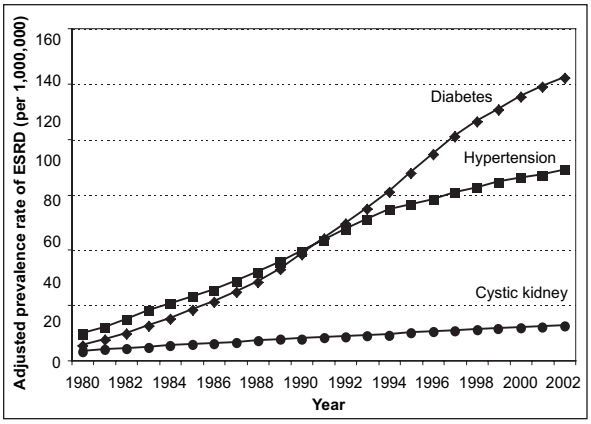

Figure 4. Point prevalent rates of report end-stage renal disease, adjusted. The prevalence of end-stage renal disease secondary to polycystic kidney disease is compared with end-stage renal disease from diabetes and hypertension. Derived from USRDS 2004 Annual Data Report.[15]

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(continued on page 625)

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