Clinical management of polycystic kidney disease

Nick Hateboer MD MRCP, Consultant Nephrologist, *Dorset County Hospital, Dorchester, Dorset*

Clin Med 2003;**3**:509–12

Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disease with renal and various extrarenal manifestations. It is one of the most common hereditary disorders, affecting approximately one in 1,000 individuals and currently accounts for 6.5% of end-stage renal disease (ESRD) in England and Wales.

Genetics

ADPKD is caused by mutations in two genes:[1,2]

- *PKD1* on chromosome 16p13.3, and
- *PKD2*, on chromosome 4q21-23.

The proteins encoded by *PKD1* and *PKD2* are polycystin-1 and polycystin-2 (Fig 1).[3] Polycystin-1 is probably involved in protein-protein or protein-carbohydrate interactions. Polycystin-2 is a nonselective cation channel that can conduct calcium ions. Mutations in either *PKD1* or *PKD2* produce identical clinical manifestations and polycystin-1 and polycystin-2 may be part of a common pathway. Although *PKD1* and *PKD2* are clinically indistinguishable, *PKD2* mutations are associated with fewer complications and a longer renal survival (Fig 2).[4]

Diagnosis

ADPKD is usually diagnosed with ultrasound. The diagnostic criteria for *PKD1* are well established[5] (Table 1). The criteria are less clear for *PKD2*, but the *PKD1* ultrasound criteria can be used for individuals older than 30. For individuals younger than 30, there is a need to be aware of occasional false negative scans. Linkage analysis can confirm or refute the diagnosis in cases of doubt, but not all families are suitable for this type of analysis, which requires the collection of DNA samples from several other living affected and unaffected family members. Screening for mutations in the large *PKD1* and *PKD2* genes by DNA sequencing is not yet readily available in the UK.

Screening

Screening of asymptomatic family members and children poses an ethical dilemma. Screening might detect a treatable complication, such as hypertension, but at present there is no cure for ADPKD and confirmation of the diagnosis can lead to a degree of stigmatisation in an otherwise healthy individual. There may be repercussions for employment and life insurance. Currently, the general consensus is to avoid screening of asymptomatic children and to wait until they reach the age of consent. Ideally, even ultrasound scanning should be preceded by genetic counselling.

Clinical features

Hypertension

Hypertension is the presenting clinical finding in 13–20% of patients and frequently develops before renal function becomes impaired. Observational studies show that faster decline in renal function is associated with hypertension, but there is no conclusive trial evidence that treatment of hypertension reduces the rate of decline.[6] Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers are known to reduce the rate of loss of kidney function in proteinuric patients with both diabetic and nondiabetic renal disease. In ADPKD (a nonproteinuric renal disease), there is no evidence that these drugs are better at protecting against decline of renal function. However, they may still have an

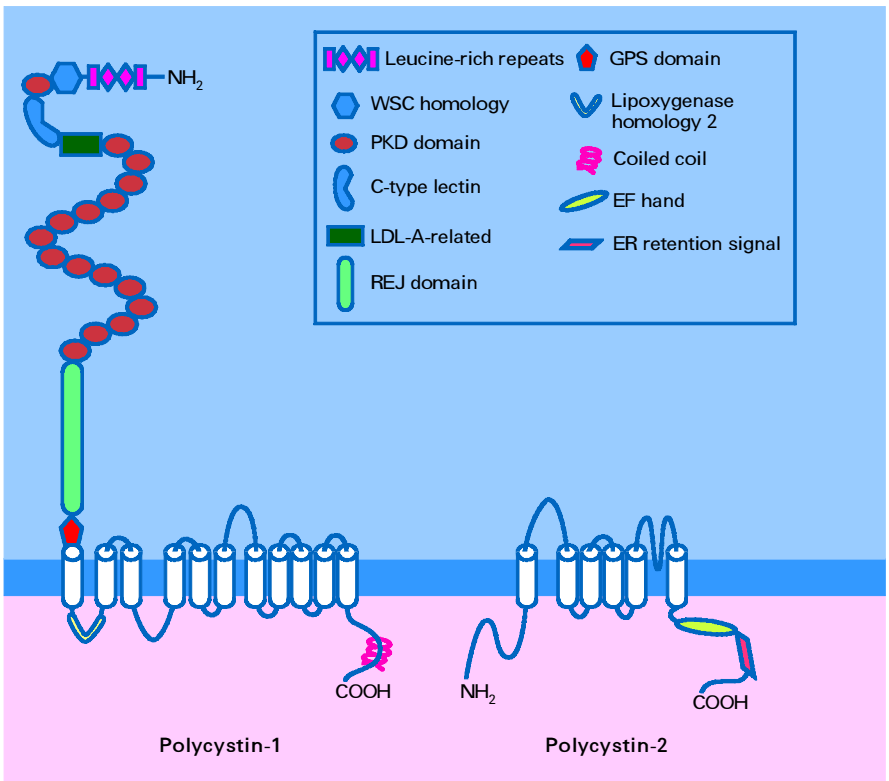

Fig 1. Structures of polycystin-1 and polycystin-2 (thick gray line = membrane bilayer; tan background = cytosol; blue background = extracellular space or endoplasmatic reticulum (ER) lumen; light grey cylinders = putative transmembrane segments) (GPS = G protein-coupled receptor proteolytic site; LDL-A = low-density lipoprotein apheresis; PKD = polycystic kidney disease; REJ = receptor egg jelly).[3]

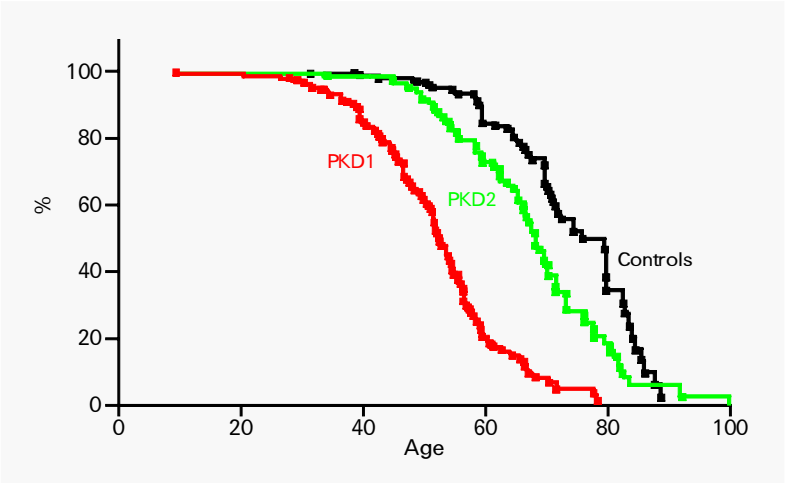

Fig 2. Survival curves to end-stage renal disease or death for *PKD1*, *PKD2* and unaffected controls (median ages and 95% confidence intervals).[4]

advantage over some other antihypertensive classes in reducing the development of left ventricular hypertrophy (LVH).

Left ventricular hypertrophy

The leading cause of death in ADPKD is cardiovascular disease.[7] LVH is well established as a risk factor for cardiovascular morbidity and mortality; its incidence is increased in ADPKD, most probably a result of early untreated hypertension. In a large, seven-year, prospective randomised study[8] comparing the impact of rigorous (<120/80 mmHg) versus standard (135–140/85–90 mmHg) blood pressure control on LVH and renal function, the former was more effective in decreasing LVH. However, as in the Modification of Diet in Renal Disease study,[6] there was no difference in renal function decline.

Haematuria

Frank haematuria is common in ADPKD. It often occurs spontaneously, but is occasionally associated with urinary tract infection, strenuous activity and, rarely, with kidney stones. The incidence is related to kidney size, the presence of hypertension and the degree of renal impairment. Gross haematuria usually ceases within several days and rarely requires specific medical or surgical intervention. Clinicians should remain wary of missing alternative causes, particularly bladder cancer.

Pain

Flank or abdominal pain is experienced by at least 50–60% of patients with ADPKD at some time during their life. Chronic pain is most probably related to cyst distension, whereas acute pain is more suggestive of intracystic haemorrhage, infection or urinary tract obstruction. Most patients with chronic pain are helped by simple analgesics, but sometimes surgical decompression or percutaneous intracystic injection of a sclerosing agent may be considered.

Renal calculi

The estimated prevalence of renal calculi in ADPKD is 11–34%, but they are often asymptomatic. Uric acid can be found in 57% of stones and calcium oxalate in 47%. Options for treatment and prophylaxis are in general the same as those for non-ADPKD stone-formers.

Table 1. Ultrasound criteria.

Age (years)	Criteria
<30	at least 2 renal cysts (unilateral or bilateral)
30–59	at least 2 cysts in each kidney
≥60	at least 4 cysts in each kidney

Infection

ADPKD is associated with an increased incidence of upper and lower urinary tract infections. It is often difficult to distinguish between pyelonephritis and renal cyst infection, but in cyst infection the urine culture is often negative and there is a poor clinical response to lipophobic antibiotics (eg aminoglycosides, beta-lactams). Lipophilic antibiotics (eg ciprofloxacin, trimethoprim) have better cyst penetration. Prolonged antibiotic therapy may be necessary, and occasionally cyst drainage or even nephrectomy may be required to control infection.

Renal failure

Kidney failure is one of the most serious complications of ADPKD. The median age for reaching ESRD is around 54 years in *PKD1* and 74 years in *PKD2*.[4] Once glomerular filtration rate falls below 50 ml/min, it will decline further at approximately 5 ml/min per year. Some individuals never develop ESRD, but conversely ESRD is occasionally seen in very young children. The treatment of ESRD is no different from that in the non-ADPKD population, with the possible exception of the occasional transplant recipient who will require a pre-emptive nephrectomy for anatomical reasons.

Fig 3. Massive cystic hepatomegaly in a patient requiring combined kidney and liver transplantation (from Ref 9 with permission).

Extrarenal manifestations

Cysts

Cysts can also be identified in the liver, spleen, pancreas and brain (arachnoid cysts) and occasionally in the oesophagus, ovaries, uterus and seminal vesicles. Liver cysts are common, with a higher prevalence in women. Pregnancy is a risk factor for massive hepatic cystic involvement (Fig 3), thought to be related to oestrogens. Some authors have therefore suggested that hormone replacement therapy should be avoided in women with liver cysts. Liver cysts are usually asymptomatic, but occasionally give rise to abdominal pain, symptoms due to compression of the gastrointestinal tract, obstructive jaundice, portal hypertension or compression of the intrahepatic vena cava.

Intracranial aneurysms

The association between ADPKD and intracranial aneurysms (ICAs) is well established. The prevalence of asymptomatic ICA in the ADPKD population is about 8%, 4–5 times higher than in the general population;[10] it may be as high as 25% among those with a family history of ICA. Rupture of ICA accounts for approximately 6% of all deaths in ADPKD[7] and also occurs at a younger age than in the general population. Screening for ICAs with magnetic resonance angiography (MRA) might be beneficial for certain categories of patients, but it remains unclear precisely who should be screened with MRA. However, there is consensus that those with a family history of brain haemorrhage should be offered screening (Fig 4).

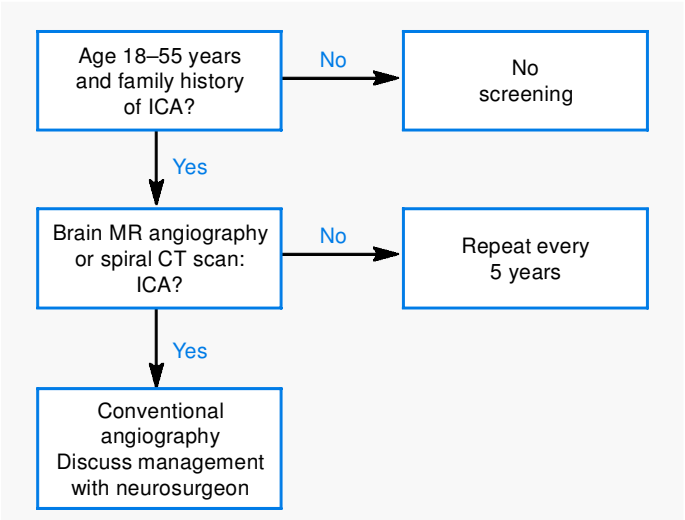

Fig 4. Algorithm for screening for intracranial aneurysm (CT = computed tomography; ICA = intracranial aneurysm; MR = magnetic resonance) (from Yves Pirson, with permission).

Cardiac valvular/cardiovascular pathology

ADPKD is associated with various cardiac valve abnormalities, including mitral incompetence, mitral valve prolapse, tricuspid incompetence, tricuspid valve prolapse and aortic incompetence. Other reported cardiovascular abnormalities in ADPKD include coronary artery aneurysms, atrial-septal aneurysms, diastolic dysfunction, dissection of the vertebral artery, aortic dissection and LVH. The prevalence of abdominal aortic aneurysms is probably not increased in ADPKD.

Hernia and other connective tissue problems

Inguinal and umbilical hernias are commonly found in ADPKD. Taken together with the valvular and cardiovascular complications, it is clear that ADPKD should be considered a connective tissue disorder with similarities to conditions like Marfan and Ehlers-Danlos syndromes.

Diverticular disease

There have been numerous case reports of complications of diverticular disease in patients with ADPKD and it has been suggested that the incidence is increased in ADPKD. However, there was a similar prevalence of diverticular disease in the patients and the healthy controls in the only controlled study in which 55 patients with ADPKD underwent a barium enema.[11]

Renal cell carcinoma

The prevalence of renal cell carcinoma (RCC) is not increased in ADPKD.[12] However, RCC is more often concurrently bilateral, multicentric and sarcomatoid in type than in the general population.[13] In addition, the diagnosis is often difficult and delayed. A recent large international study confirmed that there was no undue excess risk of kidney cancer in patients with ESRD due to ADPKD.[11]

Key Points

Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disease with various extrarenal manifestations

Subarachnoid haemorrhage from intracranial aneurysms is the most serious extrarenal complication; screening with magnetic resonance angiography should be offered to ADPKD patients with a family history of brain haemorrhage

Mutations in two different genes, *PKD1* on chromosome 16 and *PKD2* on chromosome 4 cause ADPKD. Clinically, the two conditions are indistinguishable, but overall *PKD1* is more severe

The diagnosis of ADPKD still relies on ultrasound, with clearly defined criteria according to the number of renal cysts. False negative scans occasionally occur under the age of 30

Hypertension and left ventricular hypertrophy are common early complications; cardiovascular disease is the leading cause of death in ADPKD

Kidney failure generally occurs around age 55. There is no specific treatment which is known to slow down the decline in renal function

In contrast to other renal conditions, angiotensin-converting enzyme inhibitors are not superior to other drugs in slowing progression to renal failure in ADPKD

KEY WORDS: autosound dominant, polycystic kidney

Treatment

Many dietary and pharmacological intervention strategies have been studied in humans and animals with PKD in an effort to slow the rate of renal progression. To date, no strategy has shown a consistent benefit in preserving renal function in humans with PKD.[14] More encouraging are data from a recent epidemiological study which compared survival to ESRD in patient cohorts from 1985–1992 and from 1992–2001. The latter cohort had lower blood pressures, increased use of ACEIs and slower progression of renal decline.[15]

Future prospects

New insights into the molecular genetics of ADPKD and improved understanding of the pathophysiological processes necessary for cyst development may help in the development of novel pharmacological and other interventions. An exciting discovery has been that both polycystins, 1 and 2, are expressed in renal cilia.[16] Cilia are long, thin tubular structures on the surface of renal tubular cells. Their function in human kidneys is unknown but they may have a chemosensory or mechanosensory function. This discovery has opened another avenue for research. When the function of these cilia becomes clearer, they may provide further therapeutic opportunities.

References

1 The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. The European Polycystic Kidney Disease Consortium. *Cell* 1994;**77**:881–94.

2 Mochizuki T, Wu G, Hayashi T, Xenophontos SL *et al*. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science* 1996; **272**:1339–42.

3 Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. Review. *J Am Soc Nephrol* 2002;**13**:2384–98.

4 Hateboer N, van Dijk M, Bogdanova N, Coto E *et al*. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet* 1999;**353**:103–7.

5 Ravine D, Gibson RN, Walker RG, Sheffield LJ *et al*. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet* 1994; **343**:824–7.

6 Klahr S, Breyer JA, Beck GJ, Dennis VW *et al*. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. *J Am Soc Nephrol* 1995;**5**:2037–47.

7 Fick GM, Johnson AM, Hammond WS, Gabow PA. Causes of death in autosomal dominant polycystic kidney disease. Review. *J Am Soc Nephrol* 1995;**5**:2048–56.

8 Schrier R, McFann K, Johnson A, Chapman A *et al*. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. *J Am Soc Nephrol* 2002;**13**: 1733–9.

9 Taylor JE, Calne RY, Stewart WK. Massive cystic hepatomegaly in a female patient with polycystic disease treated by combined hepatic and renal transplantation. *QJM* 1991;**80**:771–5.

10 Pirson Y, Chauveau D, Torres V. Management of cerebral aneurysms in autosomal dominant polycystic kidney disease. Review. *J Am Soc Nephrol* 2002;**13**:269–76.

11 Sharp CK, Zeligman BE, Johnson AM, Duley I, Gabow PA. Evaluation of colonic diverticular disease in autosomal dominant polycystic kidney disease without end-stage renal disease. *Am J Kidney Dis* 1999;**34**: 863–8.

12 Stewart JH, Buccianti G, Agodoa L, Gellert R *et al*. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* 2003;**14**: 197–207.

13 Keith DS, Torres VE, King BF, Zincki H, Farrow GM. Renal cell carcinoma in autosomal dominant polycystic kidney disease. Review. *J Am Soc Nephrol* 1994;**4**:1661–9.

14 Davis ID, MacRae Dell K, Sweeney WE, Avner ED. Can progression of autosomal dominant or autosomal recessive polycystic kidney disease be prevented? Review. *Semin Nephrol* 2001;**21**:430–40.

15 Schrier RW, McFann KK, Johnson AM. Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease. *Kidney Int* 2003;**63**:678–85.

16 Yoder BK, Hou X, Guay-Woodford LM. The polycystic kidney disease proteins, polycystin-1, polycystin-2, polaris and cystin, are co-localized in renal cilia. *J Am Soc Nephrol* 2002;**13**:2508–16.