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Optimising the management of polycystic kidney disease

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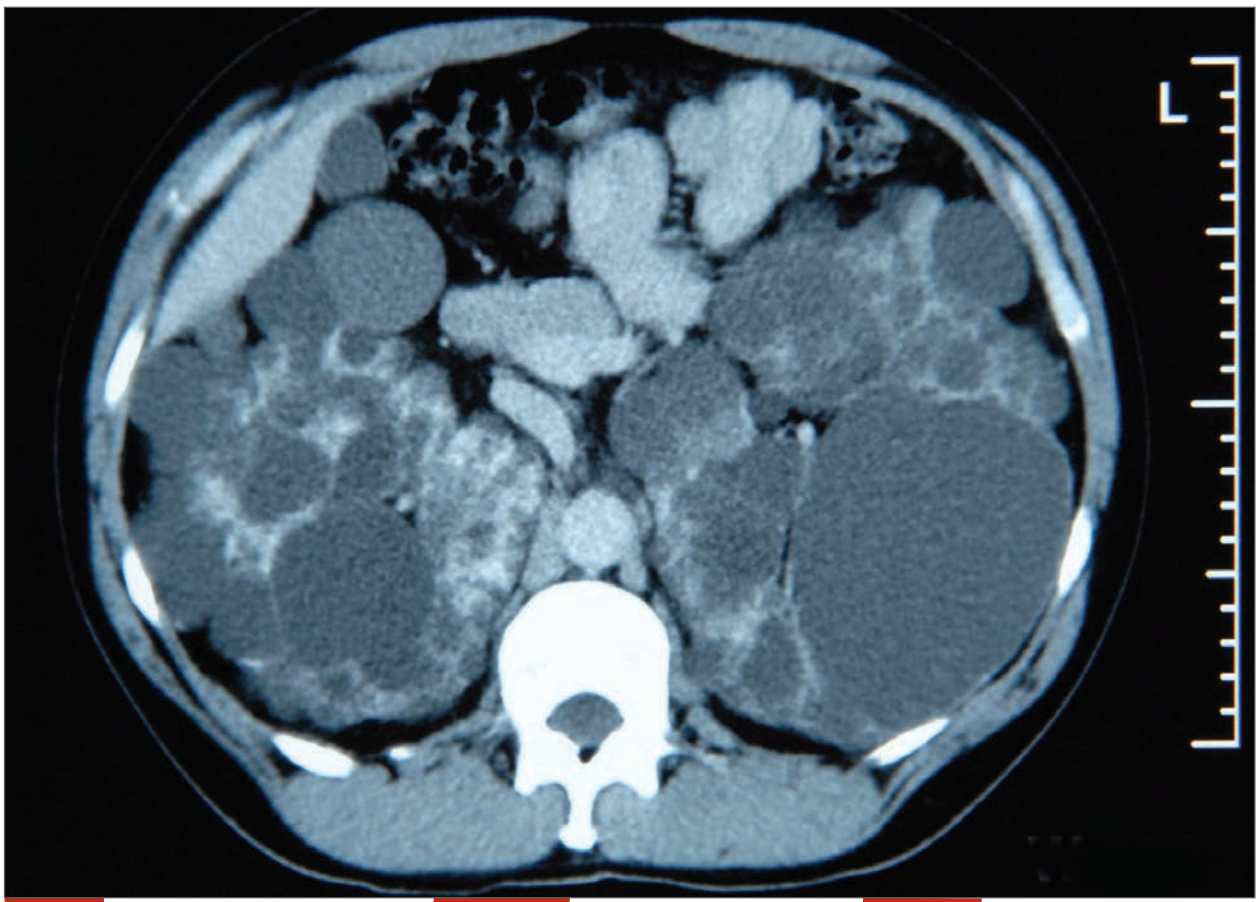


FIGURE 1
CT scan showing bilateral renal cysts and enlarged kidneys in a patient with autosomal dominant polycystic kidney disease

How should diagnosis of PKD be confirmed?

POLYCYSTIC KIDNEY DISEASE (PKD) IS THE MOST COMMON INHERITED RENAL disorder that results in chronic kidney disease. The prevalence of PKD is estimated to be between 1:500 and 1:1,000 therefore many general practices will have families with PKD registered for care.

A diagnosis of PKD should be considered in any individual with kidney cysts on an abdominal scan especially if there is a history of hypertension. PKD is associated with multiple bilateral renal cysts, slowly increasing kidney size and progressive chronic kidney disease (decline in estimated glomerular filtration rate [eGFR]). Up to 10% of adults with end-stage renal disease (ESRD), requiring chronic dialysis or kidney transplantation, have a genetic disorder such as PKD.[1]

Which patients are at increased risk of progression?

CAUSES

PKD is an autosomal dominant condition hence each child of an affected adult has a 50% chance of inheriting the disorder.[2] PKD is caused by mutations in two distinct genes encoding polycystins which are proteins important in the normal function of cell membranes lining the renal tubules and hepatic ducts.[3]

'Up to 25% of patients with PKD will have a negative family history'

Mutations in the gene PKD1 (located on chromosome 16p13.3-p12.1) account for around 85% of cases and inheritance of a PKD1 mutation is associated with an earlier onset of ESRD at a median age of 53 years. In contrast, mutations in PKD2 (located on chromosome 4q21-q23) account for around 15% of cases and are associated with a later onset of ESRD at a median age of 69 years.[3,4]

Genetic diagnostic testing is not routinely undertaken partly because »

What are the management approaches?

Table 1

Clinical features of polycystic kidney disease

Renal	Extrarenal
Haematuria (visible or non-visible)	Liver cysts and liver pain
Hypertension	Cerebral haemorrhage
Loin pain	Cardiac valve problems (e.g. mitral valve prolapse)
Cyst haemorrhage and/or cyst infections	Seminal vesicle cysts (males)
Renal calculi	Diverticulosis
Chronic kidney disease progressing to ESRD	Ovarian cysts (females)
Enlarged and palpable kidneys	Hepatomegaly

of its complexity and the associated costs of analysing the very large number of unique mutations affecting these two genes. Up to 25% of patients diagnosed with PKD will have a negative family history.[2]

PRESENTATION

PKD is a multisystem disorder of polycystin proteins with a variety of renal and extrarenal manifestations, see table 1, above. The diagnosis of PKD is often made coincidentally following radiological imaging of the abdomen. PKD can present at any age but the most common clinical features are visible haematuria, loin pain, urinary tract infection (UTI) and hypertension. Loin pain may be caused by expansion of one or more cysts, bleeding into a cyst or ureter (causing clot colic), cyst infection, UTI or renal calculi.

'It is a multisystem disorder with a variety of renal and extrarenal manifestations'

The typical clinical course of PKD is characterised by a progressive increase in both the number and size of renal cysts leading to localised pressure effects, cytokine release, inflammation with damage to neighbouring cells, fibrosis and disruption of the normal tissue architecture. This is associated with gradual loss of kidney function (falling eGFR) and progression through the stages of chronic kidney disease to ESRD.

Risk factors for progressive chronic kidney disease include:

- Younger age at diagnosis
- Large kidney volume (size) on imaging
- Rapid cyst growth
- Hypertension
- Male gender
- Visible haematuria
- Inheritance of a PKD1 versus a PKD2 mutation

Once chronic kidney disease develops the annual decline in eGFR is usually predictable and around 5 ml/min/1.73m^2.[5] Approximately 50% of individuals with PKD will require renal replacement therapy by the sixth decade of life. [2,6]

CONFIRMING DIAGNOSIS

Genetic testing to identify PKD1 and PKD2 mutations is rarely undertaken in clinical practice, unless as part of a research project. Computer tomography (CT), magnetic resonance imaging (MRI) and ultrasound sonography (USS) can all be used to identify PKD but USS is the safest and most cost-effective scan to establish the diagnosis, see figure 1, p13.

USS criteria have been published (incorporating age, number of cysts seen and whether cysts are unilateral or bilateral) to allow confirmation of a PKD diagnosis, see table 2, below.[7]

CT and MRI are both more sensitive than USS in detecting cysts as small as 0.5 cm. CT and MRI also permit assessment and serial measurement of kidney mass/size, which USS alone cannot accurately determine. Patients with larger kidney volumes (> 1,500 ml) at baseline have more rapid loss of renal function.[8]

EXTRARENAL CLINICAL FEATURES

Liver cysts

More than 80% of patients with PKD will also have multiple liver cysts. Expansion of liver cysts can lead to local pressure effects causing liver capsular pain. Liver cysts do not by themselves cause abnormal liver function tests and hepatic failure is not a clinical feature of PKD. Occasionally, infection of a liver cyst can cause serious illness requiring hospitalisation for antimicrobial therapy ± drainage of the infected cyst. Massive liver cysts are more common in women than men, particularly in those who have had multiple pregnancies, suggesting hormones may play a role in accelerating cyst growth.

Cerebral haemorrhage

Cerebral haemorrhage, secondary to rupture of an intracranial berry aneurysm, occurs in up to 8% of patients with PKD. Screening for intracranial aneurysm remains controversial and there are no universally agreed consensus guidelines. Decisions to undertake screening are usually made based on patient-specific risk factors, including a family history of intracranial aneurysm or subarachnoid

Table 2

Ultrasound criteria for the diagnosis of polycystic kidney disease, with sensitivity values, adapted from Pei et al [7]

Age (years)	PKD1 genotype	Sensitivity	PKD2 genotype	Sensitivity	Unknown genotype	Sensitivity
15-29	3 or more cysts	94.3%	3 or more cysts	69.5%	3 or more cysts	81.7%
30-39	3 or more cysts	96.6%	3 or more cysts	94.9%	3 or more cysts	95.5%
40-59	2 or more cysts in each kidney	92.6%	2 or more cysts in each kidney	88.8%	2 or more cysts in each kidney	90%
60 +	4 or more cysts in each kidney	100%	4 or more cysts in each kidney	100%	4 or more cysts in each kidney	100%

key points

SELECTED BY
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Polycystic kidney disease (PKD) is the most common inherited renal disorder that results in chronic kidney disease. PKD has an autosomal dominant pattern of inheritance. The prevalence is between 1:500 and 1:1,000. Up to 10% of adults with end-stage renal disease (ESRD) have a genetic disorder such as PKD. A family history of PKD may be absent in up to 25% of affected individuals. The most common clinical features are visible haematuria, loin pain, UTI and hypertension.

The typical clinical course is a progressive increase in the number and size of renal cysts associated with gradual loss of kidney function (falling eGFR). Risk factors for progression include: younger age at diagnosis; large kidney volume; rapid cyst growth; hypertension; male gender; and visible haematuria. Approximately 50% of individuals with PKD will require renal replacement therapy by the sixth decade of life.

PKD is a multisystem disorder associated with multiple bilateral renal cysts, slowly increasing kidney size and progressive chronic kidney disease. A diagnosis of PKD is confirmed by ultrasound scan showing the presence of multiple kidney cysts. More than 80% will also have multiple liver cysts, which can lead to local pressure effects. Cerebral haemorrhage, secondary to rupture of a berry aneurysm, occurs in up to 8% of individuals. Mitral valve prolapse occurs in up to 25% of patients. Aortic and tricuspid valve prolapse, along with aortic root dilation and ascending aortic aneurysm and dissection have all been reported in patients with PKD.

Excellent control of blood pressure is a key element in management, < 130/80 mmHg is a reasonable target using angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy. Calcium channel blockers can be added. Diuretics should not be prescribed because they are associated with fluid volume depletion and stimulation of ADH secretion. Higher levels of ADH are associated with more rapid loss of renal function.

Several drugs designed to limit cyst growth have shown promise in clinical trials (tolvaptan, octreotide, everolimus). NICE has approved the use of tolvaptan to slow the progression of cyst development in adults with PKD who have chronic kidney disease stage 2 or 3 with evidence of rapidly progressive disease. Renal replacement therapy, dialysis and transplantation, are treatment options for ESRD. Potential living related kidney donors need to be screened carefully to ensure that they do not have PKD.

haemorrhage (SAH), prior SAH, neurological symptoms, high-risk professions (such as pilots), or those undergoing major elective surgery.[9]

‘Excellent control of blood pressure is a key element in management’

Cardiac valve abnormalities

Mitral valve prolapse is the most common valvular abnormality occurring in up to 25% of patients. Aortic and tricuspid valve prolapse, along with aortic root dilation and ascending aortic aneurysm and dissection have all been reported in patients with PKD.

MANAGEMENT

Hypertension

Hypertension often develops prior to the onset of obvious chronic kidney disease. Excellent control of blood pressure is a key element in the management of patients with PKD. Non-pharmacological measures to help lower blood pressure (salt restriction, weight loss, exercise and reduction in alcohol intake) can be advised.

The rise in blood pressure is mediated in part by increased renin and angiotensin II production. For this reason blockade of the renin-angiotensin system with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is appropriate.[10] A blood pressure < 130/80 mmHg is a reasonable target and a calcium channel blocker can be added to ACEi or ARB therapy to achieve this treatment goal. More aggressive control of hypertension has not been shown to reduce the rate of eGFR decline in patients with PKD.[11]

‘Diuretics should not be prescribed for hypertension in patients with PKD’

Diuretics should not be prescribed for hypertension primarily because these drugs are associated with fluid volume depletion and stimulation of antidiuretic hormone (ADH) secretion. Higher levels of ADH are associated with faster cyst growth, increased kidney size and more rapid loss of renal function.

Drinking plenty of water to stay well hydrated and reducing consumption of caffeinated drinks is recommended to try to reduce circulating ADH levels (although there is a limited evidence base for this advice). [2]

Cyst infections

Cyst infections may present with loin pain, fever and/or septic shock and can be difficult to manage. A causative organism may not be cultured from blood or urine samples partly because the cysts usually do not communicate with the renal tracts. Infected renal cysts can be challenging to treat effectively since antibiotics may not penetrate the larger cysts. Lipid-soluble antibiotics such as ciprofloxacin are preferred as they can diffuse into cyst fluid more readily than penicillins and prolonged treatment is usually necessary to eradicate infection.[12,13]

New therapies

Several drugs (tolvaptan, octreotide, everolimus) have shown promise in clinical trials to limit cyst growth. A study of octreotide (an analogue of somatostatin), reported a smaller increase in cyst size and kidney volume in treated patients compared with those receiving placebo.[14] Short-term trials with mammalian target of rapamycin (mTOR) inhibitors, such as everolimus and sirolimus, have reported that cyst growth is reduced in patients but there were no beneficial effects on renal function.[15]

Tolvaptan, a vasopressin (ADH) receptor antagonist, is now licensed for use in adults with PKD. It reduces the rate of decline in eGFR in patients with PKD by inhibiting the binding of vasopressin (ADH) to renal tubule V2 receptors, and thus reduces cell proliferation, kidney cyst formation and fluid accumulation within cysts.

Compared with placebo, treatment with tolvaptan was associated with a modest reduction in annual rate of eGFR decline.[16] Tolvaptan, compared with placebo, had a higher frequency of adverse events because of increased aquaresis (polyuria, polydipsia, nocturia, and urinary frequency), but a lower frequency of adverse events related to PKD (kidney pain, haematuria, urinary tract infection, and back pain).

NICE has approved the use of tolvaptan to slow the progression of cyst development in adults with PKD.[17] This advice applies to patients who have chronic kidney disease stage 2 or 3 at the start of treatment, with evidence of rapidly progressive chronic kidney disease and provided that the pharmaceutical company gives a medication discount agreed in the patient access scheme.

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Treatment options for end-stage renal disease

When individuals with PKD develop chronic kidney disease then onward referral for nephrology follow-up is appropriate.

Planning for renal replacement therapy (dialysis and transplantation) is undertaken and individuals with PKD can be assessed for the option of pre-emptive kidney transplantation. If the polycystic kidneys are very large a transplant surgeon may recommend removal of one or both kidneys to provide room for a transplanted kidney. Potential living related kidney donors need to be screened carefully to ensure that they do not have PKD.

'Potential related donors need to be screened to ensure that they do not have PKD'

CONCLUSION

PKD is a common renal disorder with a variety of renal and extrarenal clinical presentations. Excellent control of hypertension and prompt treatment of cyst infections are important aspects of management. Clinical trials of novel therapies are being undertaken to delay or prevent progression to ESRD.

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Useful information

PKD charity
www.pkdcharity.co.uk

Patient.co.uk
www.patient.co.uk/health/Polycystic-Kidney-Disease.htm

NIDDK patient information
www.kidney.niddk.nih.gov/kudiseases/pubs/polycystic/

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