

# Autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease with a prevalence of 1:400 to 1:1,000 live births.<sup>1</sup> It is the most common genetic cause of renal failure, accounting for 10% of patients on dialysis. ADPKD is a systemic disorder characterised by progressive kidney enlargement, cyst formation in other organs (liver, pancreas) and non-cystic complications (arterial aneurysm).

## Genetics and pathophysiology

Inheritance of ADPKD is autosomal dominant with 100% disease penetrance. Each offspring has a 50% chance of inheriting the disease. There is a 5% rate of new mutation. Mutations in either of two genes coding for membrane proteins can lead to ADPKD:<sup>1</sup>

- PKD1 (chromosome 1613.3), 85–90% of cases, encodes for the polycystin-1 protein
- PKD2 (chromosome 4q21), 10–15% of cases, encodes for the polycystin-2 protein.

A small number of families unlinked to either gene could indicate the potential existence of a third gene (PKD3). PKD1 and PKD2 gene mutations have similar clinical phenotype, but PKD2 patients have a more favourable course. The mean age of onset of end-stage renal failure (ESRF) is 53 years for PKD1 and 69 years for PKD2. Unlike PKD1, women with PKD2 have a later onset of ESRF than men.

## Natural history

Patients are usually asymptomatic until the middle decades, but 2–5% present in childhood with significant morbidity. By the age of 60, 50% of patients with ADPKD will require renal replacement therapy. Poor prognostic indicators for renal survival include male sex, black race, haematuria before age 30, multiple pregnancies, hypertension before age 35, proteinuria, renal size and PKD1 mutation. ADPKD patients do not have a higher risk of mortality than other patients with ESRF. The main cause of mortality is cardiovascular disease (36% of cases).<sup>2</sup>

## Clinical features

### Pain

- Renal: acute pain due to infection, stones, intracystic haemorrhage and urinary tract obstruction; chronic pain due to pressure, stretching of the renal capsule or structural distortion.
- Non-renal: liver and pancreatic enlargement or infection.

### Hypertension

Hypertension is a common early finding – in 60% of patients with normal renal function.

### Urinary tract infection

About 30–50% of patients will have an episode of urinary tract infection in their lifetime.

### Cyst haemorrhage and haematuria

Gross haematuria occurs in 30–50% of ADPKD patients, with rising incidence as kidney size increases. It usually occurs spontaneously but may be related to physical activity, trauma, stones, infection or tumour.

### Nephrolithiasis

Nephrolithiasis occurs in 20–30% of patients. The presence of renal calculi should be considered if acute pain, acute

deterioration in renal function and haematuria are present.

### Massive polycystic kidneys and large renal cysts

Abdominal discomfort or pain can be caused by massive cysts. Renal cysts are not unique to ADPKD. Other potential causes are given in Table 1.

### Cancer

There is no evidence for an increased risk of renal cell carcinoma in the ADPKD population, but haematuria and flank pain with anorexia and weight loss should prompt further investigation.

### Liver cysts

Hepatic cysts are the most common extrarenal manifestation, increasing with older age (58% in the third decade and 94% in the fourth decade on magnetic resonance imaging (MRI)).<sup>3</sup> They occur more frequently and severely in females, correlating with oestrogen exposure (eg pregnancy, contraceptive pill).<sup>4</sup> They are usually asymptomatic and do not lead to hepatic failure. Pain from compression, feeling of satiety, cystic haemorrhage and infection are the most common symptoms. Rarely, massive polycystic liver disease (female preponderance) can result in portal hypertension.<sup>3</sup> Rare cases of congenital hepatic fibrosis have also been described.<sup>5</sup>

### Intracerebral aneurysms

Intracerebral aneurysms (ICA) occur in 6% of ADPKD patients without a family history of ICA and in 16% of patients with a positive family history of ICA.<sup>6</sup> However, the most common neurological event in ADPKD is hypertensive haemorrhage or ischaemic stroke.

### Symptoms of chronic kidney disease

Lethargy, poor appetite, reduced urine volume, fluid retention etc are all symptoms of chronic kidney disease (CKD).

### Pancreatic cysts

Although pancreatic cysts occur in 9% of patients older than 20 years, this is not related to pancreatic dysfunction.<sup>7</sup>

### Investigation

Table 2 lists the investigations used in assessing ADPKD patients.

New unified diagnostic ultrasound criteria for at-risk PKD1 and PKD2 indi-

viduals have recently been reported (Table 2).<sup>8</sup> The previously used criteria had a sensitivity of 100% in PKD1 patients aged 30 years or older but false-negative rates for PKD2 (23%) and PKD1 (5%) in younger patients. Where the family history is unknown or negative, these new criteria may not apply and mutation analysis may be indicated for either disease exclusion or diagnostic purposes.<sup>8,9</sup> Clinically, the presence of bilateral enlarged cystic kidneys with hepatic cysts and absence of positive extrarenal manifestations (suggesting an alternative cystic disease) make the diagnosis highly probable.

The Consortium for Radiologic Imaging Studies of PKD (CRISP) suggests that the rate of disease progression can be monitored through serial MRI kidney volume measurements prior to significant decline in glomerular filtration rate.<sup>10</sup>

**Table 1. Renal cystic diseases.**

Genetic	Non-genetic
<p>Autosomal dominant:</p> <ul style="list-style-type: none"> <li>• ADPKD</li> <li>• Tuberous sclerosis</li> <li>• Von Hippel-Lindau disease</li> <li>• Medullary cystic disease</li> <li>• RCAD</li> </ul> <p>Autosomal recessive:</p> <ul style="list-style-type: none"> <li>• ARPKD</li> <li>• Juvenile-onset nephronophthisis</li> <li>• Other rare syndromes associated with multiple malformationse</li> </ul> <p>X-linked:</p> <ul style="list-style-type: none"> <li>• Oral-facial-digital syndrome type 1</li> </ul> <p>Chromosomal disorders:</p> <ul style="list-style-type: none"> <li>• Trisomy 21</li> <li>• Trisomy 13</li> <li>• Trisomy 18</li> <li>• Trisomy C</li> </ul>	<p>Acquired:</p> <ul style="list-style-type: none"> <li>• Simple cysts</li> <li>• Acquired renal cystic disease</li> <li>• Hypokalaemia-related cysts</li> </ul> <p>Developmental:</p> <ul style="list-style-type: none"> <li>• Medullary sponge kidney</li> <li>• Multicystic dysplastic kidneys</li> <li>• Pyelocalyceal cysts</li> </ul>

ADPKD = autosomal dominant polycystic kidney disease; ARPKD = autosomal recessive polycystic kidney disease; RCAD = renal cysts and diabetes syndrome.

### Management

There is no cure for ADPKD. Treatment is aimed at blood pressure control, prompt treatment of infections and disease complications, and the management of CKD.

### Pain

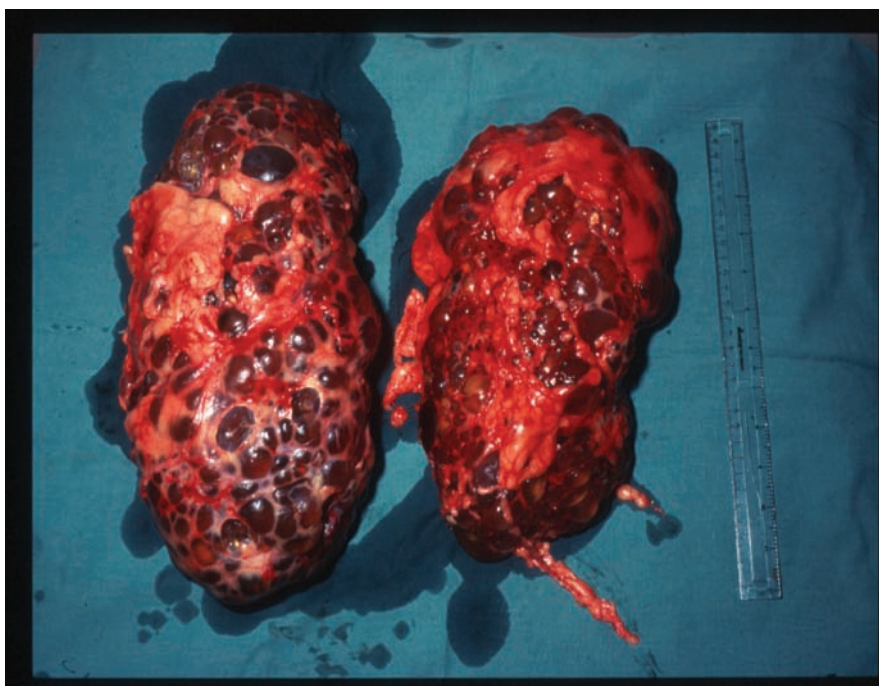
Pain should be treated with simple analgesia. Lifestyle modification and avoidance of aggravating activities can also be useful.<sup>3</sup> Patients may require pain clinic referral and surgical management (cyst decompression, renal denervation or nephrectomy).

### Hypertension

The aim is to achieve a blood pressure below 130/80 mmHg.<sup>15</sup> There is no specific evidence that any particular antihypertensive drug is more effective in ADPKD. A trial currently in progress, Halt Progression in PKD (HALT-PKD), is investigating whether the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers confers additional benefit.

### Urinary tract infection

Urine cultures may be persistently negative in cyst infection. Ureteric obstruction from stone or clot with associated infection



**Fig 1. End-stage autosomal dominant polycystic kidneys.**

should be excluded. Patients will require prompt antibiotic treatment adjusted to renal function and culture results. Cyst infection requires antibiotics that penetrate the cyst (eg macrolides, ciprofloxacin, trimethoprim etc). A prolonged course of antibiotics may be required. Surgical intervention is occasionally indicated. In the

presence of recurrent infection, it would be prudent to consider long-term prophylactic antibiotics.<sup>15</sup>

*Cyst haemorrhage and haematuria*

Conservative management with bed rest, hydration and analgesia is the mainstay of

therapy for cyst haemorrhage and haematuria as bleeding is normally self-limiting and resolves within days.<sup>15</sup> Further investigation to exclude malignancy may be considered if episodes are frequent and/or prolonged (especially in patients over 50 years old) or if other systemic symptoms are present. Rarely, haemodynamically significant bleeding can occur, requiring hospital admission, transfusion and computed tomography with or without angiography. Persistent haemorrhage may require segmental arterial embolisation (coils) or nephrectomy.

*Nephrolithiasis*

Renal stones normally resolve with conservative measures: hydration, treatment of infection and analgesia. More complicated cases should be referred for extracorporeal shockwave lithotripsy and percutaneous nephrostolithotomy.<sup>3</sup>

*Massive polycystic kidneys and large renal cysts*

Cyst reduction by alcohol sclerosis, percutaneous drainage or laparoscopic deroofing are options. Laparoscopic renal denervation can be considered in rare cases of uncontrolled pain.<sup>3</sup> Nephrectomy

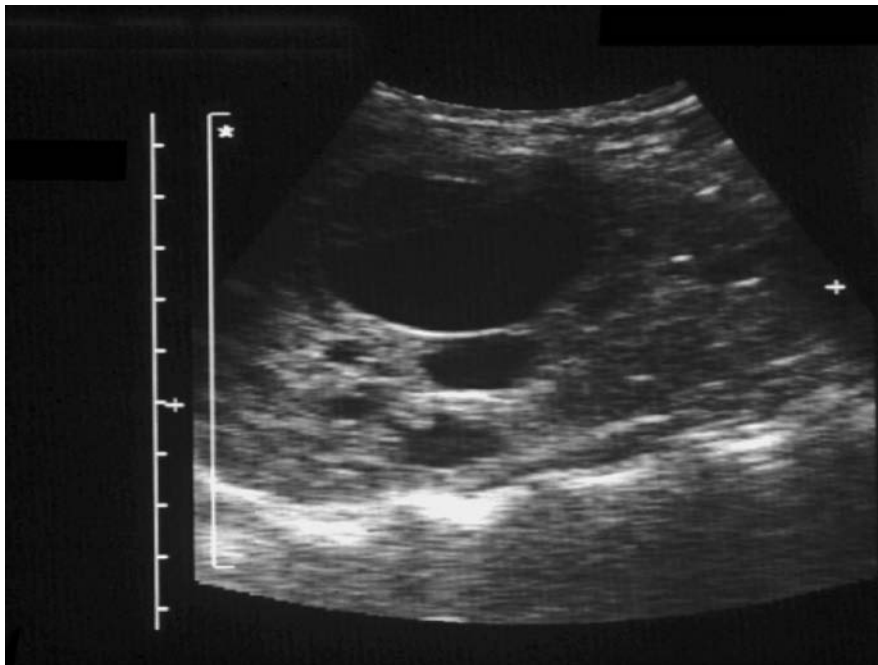


Fig 2. Ultrasound scan showing multiple cysts within the kidney.



Fig 3. Computed tomography scan showing bilateral enlarged polycystic kidneys.

**Key Points**

Autosomal dominant polycystic kidney disease is a common genetic disease due to mutations in two genes, PKD1 and PKD2

Patients may present with or develop significant extrarenal manifestations

The main aim of therapy is directed at blood pressure control, prompt treatment of infections, addressing cardiovascular risk and treating the complications of chronic kidney disease

Renal ultrasound remains the major screening method

Unified diagnostic criteria for at-risk individuals have been published

**KEY WORDS:** chronic kidney disease, genetic renal disease, intracerebral aneurysms, polycystic kidney disease, screening

is indicated for massive kidneys (occupying surgical space) in a transplant work-up, severe resistant recurrent infection, severe pain or malignancy.

### Liver cysts

Infection will require antibiotics with good cyst penetration, often given for a long course. If the infection does not settle, patients may require cyst drainage or hepatectomy in rare cases. If there are problems with satiety that impact on nutrition or severe discomfort, a surgical debulking procedure could be considered.<sup>3</sup>

### Intracerebral aneurysms

The likelihood of rupture of an aneurysm smaller than 7 mm in diameter is 0.1% per year in patients with no history of subarachnoid haemorrhage. The potential benefits of prophylactic surgery have to be balanced against the risks of the surgical complications. Conservative management is recommended for aneurysms smaller than 7 mm in the anterior circulation.<sup>16,17</sup> Larger aneurysms are treated by coil embolisation or surgical clipping.

**Table 2. Investigations.**

Laboratory studies
Serum chemistry profile, calcium and phosphate for CKD staging and monitoring
Urinalysis and culture: <ul style="list-style-type: none"> <li>• Microscopic haematuria 25%, overt proteinuria 18%</li> <li>• Nephrotic range proteinuria is rare and should prompt further investigation for concomitant glomerulonephritis</li> <li>• Sterile pyuria is common</li> </ul>
Mutation testing: <ul style="list-style-type: none"> <li>• Mutation analysis for PKD1 and PKD2 has a detection rate of up to 89%, but with a high level of unclassified variants (26–37%) and a high rate of polymorphic variants for PKD1<sup>11,12</sup></li> <li>• Mosaicism in PKD1 and a low frequency of gene deletions have recently been reported<sup>13,14</sup></li> </ul>
Imaging studies
Ultrasound: <p>Diagnostic criteria for ADPKD with positive family history:<sup>8,9</sup></p> <ul style="list-style-type: none"> <li>• ≥3 cysts in one or both kidneys in patients aged 15–39 years</li> <li>• ≥2 cysts in each kidney in patients aged 40–59 years</li> <li>• ≥4 cysts in each kidney in patients aged ≥60 years</li> </ul> <p>In sporadic cases or those with atypical features, mutation testing may be required for a positive diagnosis</p>
CT and MR imaging: <ul style="list-style-type: none"> <li>• Enhanced sensitivity for cyst detection, but not routinely used for diagnostic purposes</li> <li>• Useful in the differential diagnosis of cyst haemorrhage, renal cell carcinoma, simple cysts and renal stones</li> <li>• Serial MRI can be used to monitor the rate of kidney volume expansion<sup>10</sup></li> </ul>
MR angiography: <ul style="list-style-type: none"> <li>• Preferred imaging technique for diagnosing ICA<sup>6</sup></li> <li>• Screening is recommended in patients with:               <ul style="list-style-type: none"> <li>–family history of ICA</li> <li>–symptoms of ICA</li> <li>–a high-risk occupation eg airline pilot</li> <li>–previous ICA</li> </ul> </li> <li>• Routine screening of asymptomatic ADPKD patients is not recommended</li> </ul>
ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; CT = computed tomography; ICA = intracerebral aneurysm; MRI = magnetic resonance.

If an aneurysm larger than 7 mm in diameter is detected, follow-up surveillance scans will be required.<sup>17</sup> Control of hypertension and hyperlipidaemia, and termination of smoking are advised. The risk of a new aneurysm developing after an initial negative study is about 2.6% at 10 years in patients with a positive family history of ICA.<sup>18</sup>

### Chronic kidney disease and renal replacement therapy

Both peritoneal dialysis and haemodialysis can be used in ADPKD patients. Transplantation is the treatment of choice but pre-emptive nephrectomy may be required if kidneys are massively enlarged. There is no difference in patient or graft survival in ADPKD patients compared with other ESRF populations.<sup>15</sup> However a threefold increased risk of developing new-onset diabetes after transplantation in ADPKD has recently been reported.<sup>19</sup>

### Family screening

Patients should be advised to inform at-risk blood relatives of the diagnosis and the need for screening. At consultation, the inheritance pattern should be explained, with advice on methods of presymptomatic diagnosis, including the possibility of prenatal diagnosis. Each at-risk individual should be informed of the consequences of diagnostic screening, including the possibility of false-negative ultrasound tests in younger patients.

### Making a decision to diagnose

#### Pros

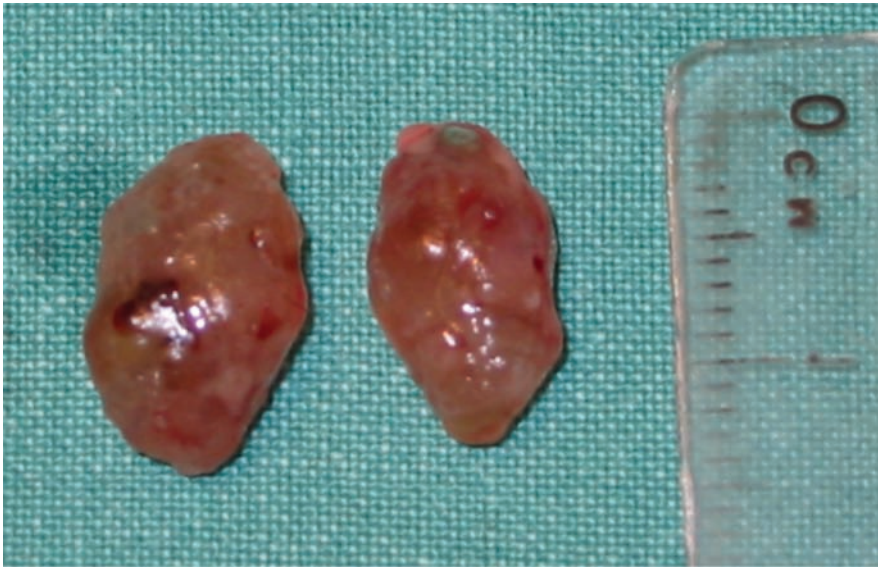
- early management of complications
- family planning
- absence of ADPKD reassures patient.

#### Cons

- psychological consequences as no specific treatment or cure is available at present
- insurance and employment issues.

Family members who opt not to have screening should be advised to have





**Fig 4. Pathological specimen of PKD2 knockout mouse kidneys showing kidney enlargement due to multiple cysts.**

yearly checks on renal function, blood pressure and urinalysis, and to inform their general practitioner of their risk of developing ADPKD.

### Pregnancy

There should be preconception counselling and referral to specialist renal and obstetric services. Prenatal diagnosis by chorionic villous sampling can be done at the ninth week of pregnancy. This is not performed routinely due to high intrafamilial phenotypic variability. Prenatal screening may be considered in families with one severely affected child (early-onset PKD) who have a calculated 45% recurrence risk for following pregnancies.<sup>20</sup>

The risk of worsening renal function and complications in pregnancy are higher in the presence of moderate-to-severe renal impairment, proteinuria and hypertension. Hypertensive complications, including new and worsening hypertension, have been reported in 25% of patients, with pre-eclampsia in 11%.

### Future prospects

Several promising candidate drugs have commenced phase 3 clinical trials, based largely on their efficacy in rodent

models of PKD:

- A multicentre trial of tolvaptan, a vasopressin type 2 receptor antagonist, commenced in 2007.<sup>21</sup>
- Octreotide, a somatostatin analogue,<sup>22</sup> has been shown to inhibit kidney growth in a small phase 2 crossover study.
- Rapamycin,<sup>23</sup> phase 3 clinical trials of sirolimus and everolimus (a derivative of rapamycin) have commenced.

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## NCC-CC GUIDELINES

# Chronic kidney disease

National clinical guideline for early identification and management in adults in primary and secondary care

Chronic kidney disease (CKD) is of growing importance in the UK. The NHS is increasingly focusing on prevention and on the early detection and treatment of this potentially progressive disease, while the prevalence of risk factors for CKD, such as diabetes, obesity and hypertension, is rising.

In commissioning this guideline, the Department of Health was clear that its focus should be early detection and management. This is the area where the guideline can deliver its greatest potential benefit, by delaying progression of disease and therefore reducing the need for dialysis or transplant. The key recommendations singled out in the guideline reflect this emphasis. They present clear criteria for testing for CKD, for suspecting progressive CKD, and for referring people for specialist assessment, all of which will be useful in primary care. Recommendations are also provided on starting treatment once proteinuria has been assessed. As well as providing a comprehensive guide to the identification and management of patients with CKD for general practitioners and general physicians, the guideline will also be relevant to nephrologists, diabetologists, nurses, clinical biochemists and other health professionals involved in the care of patients with CKD.

Healthcare professionals in primary care are taking on an increasing role in the management of CKD; and this guideline provides a single useful and accessible reference promoting a consistent high quality of care, and an improved quality of life, for longer, for people with CKD.



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