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Dr Patrick Linden
MB BCh MPH MRCP
Specialist Trainee in Renal Medicine

Dr Christopher Hill
MD FRCP
Consultant Nephrologist

Regional Nephrology Unit,
Belfast, UK

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AUTHORS
Dr Patrick Linden
MB BCh MPH MRCP
Specialist Trainee in Renal Medicine

Dr Christopher Hill
MD FRCP
Consultant Nephrologist

Regional Nephrology Unit, Belfast, UK

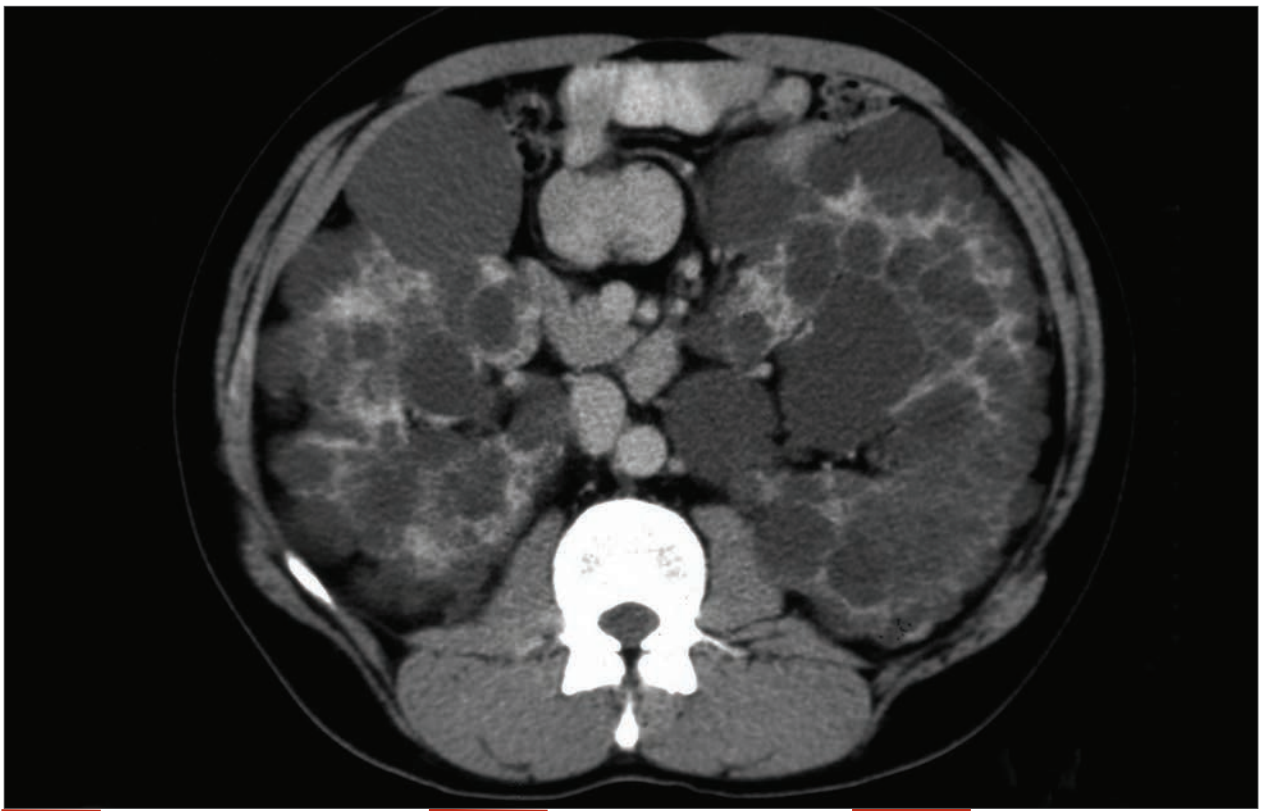


FIGURE 1
CT scan of bilateral renal cysts and enlarged kidneys in polycystic kidney disease

How does polycystic kidney disease present?

POLYCYSTIC KIDNEY DISEASE (PKD) IS THE MOST COMMON CAUSE OF INHERITED KIDNEY DISEASE worldwide.

A recent meta-analysis estimated prevalence as < 5 per 10,000 population.[1] Despite being a rare disease it accounts for 7% of cases of end-stage renal disease (ESRD) in the UK annually.[2]

PKD can be asymptomatic and should be considered in any patient with renal cysts noted on abdominal imaging, especially if they have a history of hypertension.

PKD is a genetic disorder with an autosomal dominant mode of inheritance, hence any child of an affected parent has a 50% chance of inheriting the condition.[3] Despite this 25% of patients will have no known family history and these cases are thought to be due to de novo mutations in the causative genes.[3]

What are the potential complications?

'Polycystic kidney disease can be asymptomatic and should be considered in any patient with renal cysts noted on abdominal imaging'

PKD is caused by mutations in the genes coding polycystins, proteins involved in the function of cell membranes of renal tubules and other organs.[4]

What are the management strategies?

The vast majority (95%) of cases are caused by one of two gene mutations. Mutation of the PKD1 gene (located on chromosome 16) accounts for around 80%, while mutation of the PKD2 gene (located on chromosome 4) accounts for around 15%.[5]

The PKD1 mutation is associated with a more aggressive phenotype. Median age at onset of ESRD is 54 years for patients with a PKD1 mutation compared with 69 years for patients with a PKD2 mutation.[6]

However, considerable variation is seen, even within families with the same mutation, suggesting that other environmental factors may also influence disease progression.

PRESENTATION

PKD is a multisystem disease characterised by renal and extrarenal »

features (see table 1, below), however in the early stages it can be asymptomatic. It can present in a variety of ways.

Incidental finding

Multiple renal cysts may be seen on radiographic scans performed for alternative indications. The ultrasound criteria for the diagnosis of PKD are summarised in table 2, below, and are dependent upon the number of cysts and their distribution between both kidneys.[7]

Family history

Given the inherited nature of PKD, patients may present requesting investigation for diagnosis prior to the onset of symptoms. A general practice may have several generations of an affected family on its register.

Table 1

Clinical features of polycystic kidney disease

Renal
- Haematuria (visible or non-visible)
- Hypertension
- Loin pain
- Cyst haemorrhage and/or cyst infections
- Renal calculi
- Chronic kidney disease progressing to end-stage renal disease
- Enlarged and palpable kidneys

Extrarenal
- Liver cysts and liver pain
- Cerebral haemorrhage
- Cardiac valve problems (e.g. mitral valve prolapse)
- Seminal vesicle cysts (males)
- Diverticulosis
- Ovarian cysts (females)
- Hepatomegaly

Hypertension

Patients with PKD may present with hypertension before a decline in eGFR is noted.

Chronic kidney disease (CKD)

As PKD progresses there is gradual loss of kidney function, with a predictable decrease in eGFR (falling annually by up to 5 ml/min/1.73m^2).[8] CKD may be identified on routine blood tests performed for other reasons.

The size and number of renal cysts will continue to increase with time leading to localised pressure effects and damage to surrounding normal renal parenchyma.

Risk factors for more rapid progression include younger age at diagnosis, large kidney volume, hypertension, male gender, visible haematuria and inheritance of a PKD1 mutation.

Cyst complications

Cysts and their complications account for many of the symptoms that patients experience. Cyst haemorrhage, rupture or infection can all present with acute loin pain. Infections can be severe and associated with systemic upset and sepsis. Bleeding can occur into cysts and as a result may not be 'visible' but can be sufficiently severe to cause symptomatic anaemia. Visible haematuria can occur in the setting of cyst rupture or haemorrhage if the involved cyst communicates with the urinary tract.

DIAGNOSIS

Both PKD genes are very large and many mutations are described in each gene. This makes routine genetic testing difficult. It is often unnecessary in those with a family history of PKD. Genetic testing may be considered in patients who have no family history, younger relatives of affected individuals who wish to become kidney donors or patients who have features of other renal cystic disorders.

DNA sequencing techniques are rapidly evolving, and it may soon be possible to offer routine DNA sequencing for PKD patients.

At present, diagnosis is primarily made on the basis of ultrasound sonography showing evidence of renal cysts[7] (see table 2, below) and family history. Computerised tomography (CT), see figure 1, p17, and magnetic resonance imaging (MRI) can also be used to identify smaller cysts as they can achieve much greater resolution than ultrasound. However, these imaging modalities are not routinely used for diagnosis.

'Greater increases in total kidney volume have been associated with faster decline in eGFR'

MRI measurement of the total kidney volume is a novel technique. Greater increases in total kidney volume have been associated with faster decline in eGFR.[9]

COMPLICATIONS

PKD can cause a number of extrarenal complications.

Liver cysts

In addition to renal cysts, cysts can also develop in other organs. The liver is by far the most common site for extrarenal cysts affecting around 80% of PKD patients.

Cysts can cause liver capsular pain, early satiety, nausea and vomiting.[10] They rarely compromise hepatic function but can become infected and may require extended courses of antibiotics.

Intracranial aneurysms

Intracranial haemorrhage due to rupture

Table 2

Ultrasound criteria for the diagnosis of polycystic kidney disease in patients with a positive family history, 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

Dr Phillip Bland
Former GP, Dalton-in-Furness, UK

Polycystic kidney disease (PKD) is the most common cause of inherited kidney disease worldwide. It has a prevalence of < 5 per 10,000 population and accounts for 7% of cases of end-stage renal disease (ESRD) in the UK. PKD is a genetic disorder with an autosomal dominant mode of inheritance; hence any child of an affected parent has a 50% chance of inheriting the condition. Despite this 25% of patients will have no known family history and these cases are thought to be due to de novo mutations in the causative genes. Routine genetic testing is often unnecessary in those with a family history of PKD. Diagnosis is primarily made on the basis of a positive family history plus an age-specific minimum number of cysts on ultrasonography.

PKD can present asymptomatically and should be considered in any patient with renal cysts noted on abdominal imaging, especially if there is a history of hypertension. Patients with PKD may present with hypertension before a decline in eGFR is noted. As PKD progresses there is gradual loss of kidney function, with a predictable decrease in eGFR.

Cyst haemorrhage, rupture or infection can all present with acute loin pain. Infections can be severe and associated with systemic upset and sepsis. Bleeding can occur into cysts and as a result may not be 'visible' but can be sufficiently severe to cause symptomatic anaemia. Visible haematuria can occur in the setting of cyst rupture or haemorrhage if the involved cyst communicates with the urinary tract.

PKD can cause a number of extrarenal complications. Liver cysts affect around 80% of PKD patients and can cause liver capsular pain, early satiety, nausea and vomiting. Intracranial haemorrhage due to rupture of an intracranial berry aneurysm is a potentially life-threatening complication of PKD and should be considered in any patient presenting with thunderclap headache, new focal neurology or unexplained syncope. Mitral valve prolapse is common and other valvular and aortic abnormalities can occur.

Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are the first choice antihypertensive agents in PKD. The target clinic blood pressure should be < 130/80 mmHg. Lipid-soluble antibiotics, such as ciprofloxacin, are effective for cyst infections as they achieve better cyst penetration than non-lipid soluble agents. Tolvaptan, a vasopressin receptor antagonist, can be used in some PKD patients and can slow cyst development and the rate of decline in renal function.

The median age at onset of ESRD is 54 years for patients with a PKD1 mutation compared with 69 years for patients with a PKD2 mutation. Planning for renal replacement therapy (kidney transplant or dialysis) should start well in advance of the onset of ESRD.

of an intracranial berry aneurysm is a potentially life-threatening complication of PKD and should be considered in any patient presenting with thunderclap headache, new focal neurology or unexplained syncope. The prevalence of aneurysms increases with age and they may be present in as many as 20% of patients over 60 years.[11]

Despite their prevalence there is no consensus on screening for intracranial haemorrhage in PKD patients. Screening is considered on an individual patient basis particularly if there are risk factors such as a strong family history of subarachnoid haemorrhage and/or neurological symptoms.

Cardiovascular abnormalities

Cardiac valvular abnormalities are frequently associated with PKD. Mitral valve prolapse is the most common abnormality although other valvular and aortic abnormalities can occur.

Fertility and pregnancy

Female fertility is not impaired unless patients have advanced CKD. Male fertility may be impaired if there are cysts in the seminal vesicles or prostate. Pregnancy can be complicated by higher rates of hypertension, pre-eclampsia, preterm birth and progression of CKD so prepregnancy counselling is recommended. Counselling should include discussion about the risk of transmission of PKD to offspring.

Psychological impact

PKD is a chronic, progressive disease that impacts on patients' mental health as well as their physical health.[12] A UK study found that 22% of PKD patients had evidence of depressive symptoms.[13] Patients are living with a disorder that they may have seen other family members suffer from. They may fear progressive CKD and the risk of needing dialysis or transplantation in the future.

Patients often live with chronic pain caused by their renal and liver cysts and analgesic options may be limited in those with more advanced CKD.

MANAGEMENT

Hypertension

Tight blood pressure control is one of the cornerstones of PKD management. Hypertension frequently occurs prior to any reduction in eGFR in PKD. Adopting a healthy lifestyle (weight loss, low salt diet, exercise and reduction in alcohol intake) should be advised. However, pharmacological treatment will usually be required at some point.

Angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) are the first choice antihypertensive agents in PKD. Hypertension in PKD is partly mediated by excess renin and angiotensin II. Patients should be commenced on either an ACEi or ARB and it should be gradually titrated up to the maximum tolerated dose.[14]

'Hypertension often occurs prior to any reduction in eGFR in polycystic kidney disease'

Treatment should be aimed at achieving a clinic blood pressure < 130/80 mmHg. Calcium channel blockers can be added as a second-line agent.

ADH secretion appears to stimulate more rapid cyst growth, increase in kidney volume and faster decline in eGFR in PKD. Although thiazide or thiazide-like diuretics are normally used as third-line antihypertensive therapy in other patients with hypertension they should be avoided in PKD. Thiazides (and other diuretics) cause volume depletion and stimulate excess ADH secretion. In contrast, PKD patients are advised to maintain a high fluid intake to suppress ADH as much as possible.

Cyst infections

Cyst infections can be difficult to distinguish from simple cyst rupture or haemorrhage as they can all cause loin pain. However, cyst infection is associated with persistent pain, systemic symptoms and signs (e.g. pyrexia) or even septic shock.

Infections can be difficult to eradicate as cysts are 'walled off' from the renal parenchyma and do not communicate with the urinary tract. Lipid-soluble antibiotics, such as ciprofloxacin, are effective treatments for cyst infections as they achieve better cyst penetration than non-lipid soluble agents.[15]

Disease specific agents

As discussed earlier, ADH (vasopressin) stimulates accelerated cyst growth and faster decline in renal function. Tolvaptan specifically blocks the vasopressin (V2) receptor in the kidney. In a large randomised controlled trial, tolvaptan reduced the rate of increase in kidney volume and also reduced the rate of loss of renal function.[9] Due to its »

mechanism of action, the most common side effects noted were thirst and polyuria.

Tolvaptan therapy can also affect liver function, therefore monthly monitoring with liver function tests is required for the first 18 months of treatment. NICE published guidance on tolvaptan in 2015 and approved its use in patients with PKD who have CKD stage 2 or 3 (eGFR > 30 ml/min/1.73m^2) and evidence of rapidly progressive renal disease.[16]

Surgical intervention

Surgery is rarely required in PKD. Occasionally, very large cysts may be deroofed if they are causing chronic pain although it can often be difficult to identify one causative cyst among a mass of others.

In a small number of cases, kidney size may be so massive that there is no space left in the abdomen for a transplant. Nephrectomy can be considered in this situation although this can result in patients with poor baseline renal function needing to start dialysis. For this reason, if nephrectomy is required, it is usually deferred until the patient has commenced dialysis.

End-stage renal disease

Many patients will eventually progress to ESRD. Planning for renal replacement therapy (kidney transplant or dialysis) starts well in advance of this occurring. Ideally, if the patient has a suitable live donor available then they can be transplanted before requiring dialysis (preemptive transplantation).

However, if they have no suitable live donor then a period of dialysis therapy may be required while awaiting a deceased donor transplant. Kidney transplantation (live donor and deceased donor) is associated with excellent outcomes in PKD.[17]

CONCLUSION

PKD is the most common inherited cause of ESRD. It is associated with multisystem complications as well as progressive CKD. Management includes tight blood pressure control, prompt treatment of complications such as cyst infections and, in some cases, use of tolvaptan to slow progression of CKD.

Competing interests: None

REFERENCES

1 Solazzo A, Testa F, Giovanella S et al. The prevalence of autosomal dominant polycystic kidney disease (ADPKD): A meta-analysis of European literature and prevalence evaluation in the Italian province of Modena suggest that ADPKD is a rare and underdiagnosed condition. *PloS One* 2018;13(1):e0190430
2 UK Renal Registry (2020). UK Renal Registry 22nd Annual Report. https://renal.org/audit-research/annual-report
3 Grantham JJ. Autosomal dominant polycystic kidney disease. *N Engl J Med* 2008;359:1477-85
4 Hildebrant F, Benzing T, Katsanis N. Ciliopathies. *N Engl J Med* 2011;364:1533-43
5 Chapman AB, Devuyst O, Eckardt KU et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2015;88:17-27
6 Reed BY, McFann K, Bekheirnia MR et al. Variation in age at ESRD in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2008;51:173-83
7 Pei Y, Obaji J, Dupuis A et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;20:205-12
8 Klahr S, Breyer J, Beck G et al. Dietary protein restrictions, 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
9 Torres VE, Chapman AB, Devuyst O et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012;367:2407-18
10 van Gulick JJM, Gevers TJG, van Keimpema L, Drenth JPH. Hepatic and renal manifestations in autosomal dominant polycystic kidney disease: a dichotomy of two ends of a spectrum. *Neth J Med* 2011;69:367-71
11 Xu HW, Yu SQ, Mei CL, Li MH. Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. *Stroke* 2011;42:204-06
12 EAF co-chairs, Harris T, Sandford R et al. European ADPKD forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD forum and multispecialist roundtable participants. *Nephrol Dial Transplant* 2018;33:563-73
13 Simms RJ, Thong KM, Dworschak GC, Ong ACM. Increased psychosocial risk, depression and reduced quality of life living with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2015;31:1130-40
14 Torres VE, Abebe KZ, Chapman AB et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med* 2014;371:2267-76
15 Sklar AH, Caruana RJ, Lammers JE, Strauser GD. Renal infections in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 1987;10:81-88
16 National Institute for Health and Care Excellence. TA358. Tolvaptan for treating autosomal dominant polycystic kidney disease. NICE. London. 2015 www.nice.org.uk/guidance/ta358
17 Kanaan N, Devuyst O, Pirson Y. Renal transplantation in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol* 2014;10:455-65

Useful information

For patients

Polycystic Kidney Disease charity
www.pkdcharity.co.uk/

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

NIDDK
www.niddk.nih.gov/health-information/kidney-disease/polycystic-kidney-disease/what-is-pkd

Edinburgh Renal Unit
https://edren.org/ren/edren-info/polycystic-kidney-disease-pkd

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