Polycystic Kidney Disease

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Contents

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Learning Objectives

1. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of the end-stage renal disease (ESRD).
2. ADPKD is a systemic disorder caused by either a *PKD1* or *PKD2* gene mutation that results in progressive cystic kidney enlargement.
3. The *PKD1* and *PKD2* genes encode the proteins polycystin 1 and polycystin 2 respectively. Polycystins are integral components of renal tubular cilia.
4. Knowledge of the pathophysiology of ADPKD has been translated into novel therapies being tested in clinical trials. Tolvaptan is now licensed for the treatment of patients with ADPKD.
5. The steady progression of ADPKD to ESRD over many years allows for optimal planning by multidisciplinary teams for eventual renal replacement therapy.

60.1 Introduction

Polycystic kidney disease is a Mendelian autosomal dominant disorder that is estimated to affect more than 12 million people worldwide and is responsible for up to 10% of patients with end-stage renal disease (ESRD) [1–4]. At-risk individuals with a family history of the disorder have a 50% chance of inheriting polycystic kidney disease [1]. It represents a major public health burden and is associated with reduced quality of life (QoL) [5, 6]. Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development and growth of multiple renal cysts resulting in a gradual increase in kidney size and associated hypertension [1, 7]. The enlarged kidneys may become symptomatic secondary to painful cyst expansion, haematuria, infection, and nephrolithiasis. ADPKD is a systemic disorder with other organ involvement including polycystic liver disease and a higher risk of cerebral haemorrhage from associated intracranial aneurysms [8].

Chronic kidney disease develops because the kidney cysts expand and destroy much of the renal parenchyma resulting in loss of nephrons [1, 7]. Glomerular hyperfiltration can maintain a relatively normal glomerular filtration rate into later adulthood when renal failure develops. ADPKD is not typically associated with elevated urinary protein excretion [9]. Unfortunately, no treatment has been proven to extend renal survival [1]. Improved understanding of the cell biology and pathophysiology of ADPKD is informing the design of clinical trials to establish if novel drugs can delay progression to ESRD [1, 7, 10].

> Autosomal dominant polycystic kidney disease is a systemic disorder characterized by gradual cystic enlargement of both kidneys and is associated with slowly progressive chronic kidney disease in adults

60.2 Clinical Features

The spectrum of presentation of ADPKD is wide and includes both renal and extra-renal features.

60.2.1 Kidney Involvement

ADPKD can be discovered incidentally following imaging tests for other indications or following an ultrasound scan in persons with a positive family history who have requested screening (Figs. 60.1 and 60.2). Hypertension typically emerges in early adulthood and usually prior to the obvious increase in kidney size on clinical examination [11]. The hypertension is in part due to distortion of the renal microvasculature by cysts leading to activation of the renin-angiotensin-aldosterone system [11]. Other asymptomatic findings include urinary dipstick abnormalities (non-visible haematuria, proteinuria and/or leucocytes) and as a later feature the presence of abnormal renal function (elevated serum creatinine and reduced eGFR) [12].

Renal cysts may be symptomatic resulting in loin pain secondary to infection or haemorrhage resulting in rapid cyst expansion [1, 7]. Visible haematuria may be secondary to cyst rupture or kidney stone disease [12,

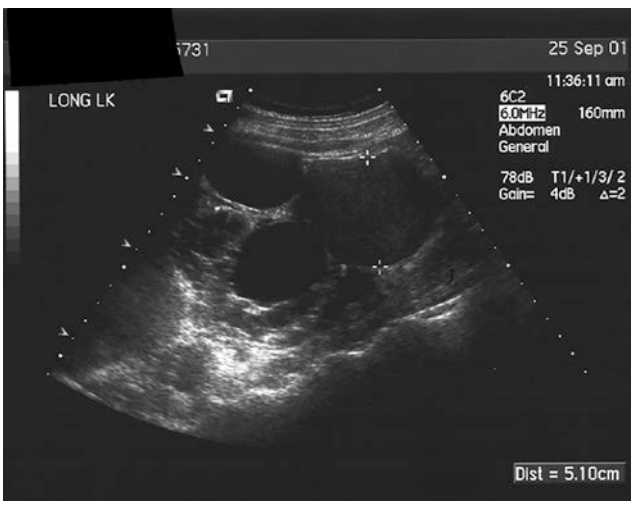

Fig. 60.1 Ultrasound scan of polycystic kidney. The scan demonstrates numerous fluid-filled renal cysts of varying diameter

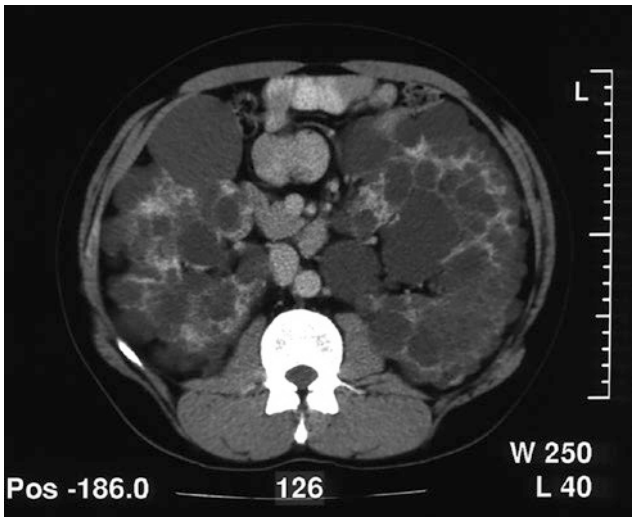

Fig. 60.2 CT scan of the abdomen. Massively enlarged polycystic kidneys occupy most of the abdominal cavity

13]. The cysts of PKD are not premalignant but can make the investigation and diagnosis of a coincidental renal cancer challenging, and malignancy should be considered if older patients present with new-onset haematuria.

The development of abnormal kidney function tends to be a later feature of ADPKD although several factors are reported to be associated with an earlier decline in GFR. These include inheritance of a *PKD1* mutation versus a *PKD2* mutation (as cysts develop earlier in persons with the *PKD1* genotype), a younger age at ADPKD diagnosis, hypertension from a younger age, male sex, hyperlipidaemia, sickle cell trait, large kidney volumes at diagnosis, and visible haematuria [14, 15]. Low birth weight may also be an independent risk factor [16]. When counselling individuals, it is often helpful to determine when any affected relatives were diagnosed or required renal replacement therapy. This can help when discussing the prognosis and possible requirement for renal replacement therapy. Unfortunately, this is not a completely reliable guide as there can be considerable variation in age at onset of ESRD, even between family members with the same documented *PKD* mutation [1, 8]. This heterogeneity in clinical course reflects modifying contributions from other genes as well as environmental factors that may be triggering the somatic mutational 'hits' on the normal copy of the *PKD* gene. At present, there are no useful urinary or plasma biomarkers, other than serum creatinine, that reliably predict the risk of progression in ADPKD [17]. Measurement of total kidney volume by MRI is a promising imaging biomarker to help predict progression to ESRD [8, 18].

60.2.2 Other Organ Involvement in ADPKD

Extra-renal features include cysts in other organs, most commonly the liver, but also in the pancreas, spleen, arachnoid membranes, and seminal vesicles. There is no relationship between ADPKD and polycystic ovarian syndrome [19].

Polycystic liver disease (PLD) is the most common extra-renal manifestation of ADPKD (present in up to 83% of affected individuals), and hepatic cysts can cause massive liver enlargement with abdominal pain, distension, early satiety, nausea, and vomiting [20]. It is uncommon for liver function tests (LFTs) to be abnormal due to the presence of cysts alone, and so alternative explanations such as liver cyst infection or biliary tract obstruction should be sought if elevated LFTs are detected [20, 21]. Symptoms of hepatic pain, compression of the inferior vena cava, or recurrent infection may require surgery [20]. Interestingly, women tend to have more severe liver cyst involvement than men, with multiparity and oestrogen exposure being recognised risk factors for PLD [1].

Intracranial aneurysms (ICAs) are perhaps the most feared extra-renal complication of ADPKD with the prevalence of ~5% in younger adults rising to over 20% in persons over 60 years of age [22, 23].

Patients with a family history of ICA or subarachnoid haemorrhage appear to be at greatest risk for ICA rupture [8, 24]. Screening for ICA remains controversial; definite indications for screening with MRI or CT include a personal or family history of rupture, presence of warning symptoms such as a headache or focal neurological deficit or for those in whom a loss of consciousness while working would place them or others at serious risk of harm [8]. At present screening is not recommended outside of these scenarios unless the patient requests an investigation. If an ICA is larger than 7–10 mm, there is an increased risk of rupture, but smaller ICAs are generally safely managed by interval scanning [25]. Intervention for smaller, asymptomatic ICAs is not without danger. The risk-benefit ratio of intervention mandates individual discussion with neurosurgical colleagues and careful explanation to patients. There are no randomised trials to determine the risk-benefit ratio of screening for ICA [26].

Other extra-renal manifestations of PKD include an increased risk of abdominal herniae (especially in those who elect to perform peritoneal dialysis), colonic diverticula, and various cardiac valvular lesions, the most common being mitral valve prolapse which occurs in up to 25% of persons with ADPKD [1, 8]. Occasional case reports of thoracic aortic aneurysms

have been published, and it is worth bearing this in mind if a patient presents with back pain, hypotension, or chest pain for which no other obvious cause is apparent [27].

Fertility is not affected by the presence of ADPKD unless renal function is severely compromised. Women with normal blood pressure and renal function usually have uncomplicated pregnancies, but those with hypertension are at an increased risk of pre-eclampsia and progressive chronic kidney disease and so should receive counselling, ideally pre-conceptually, with an early discussion between nephrologists and obstetricians [28]. Hypertension should be managed using drugs that are not obviously teratogenic. Seminal or prostatic cysts can affect male fertility.

The ***psychological impact*** of living with ADPKD can easily be overlooked [5]. Some individuals may consider themselves as having an incurable illness or may fear rapid progression to ESRD, especially if other family members required renal replacement therapy at a young age [29]. The presence of chronic pain or discomfort from polycystic organs may contribute to depression [30]. Uncertainty concerning the prognosis of younger family members or children can also be a source of considerable psychosocial stress. Studies that incorporate the psychological impact of APDKD as part of the patient-reported outcome measures are important [31]. Patients should be counselled about the management of chronic pain and advised not to use NSAIDs and to limit dependence on opiates. The addition of a tricyclic antidepressant may be useful for both depression and pain.

60.3 Epidemiology

ADPKD affects all races equally with a frequently quoted prevalence of 1:400 to 1:1000 [32]. A more recent estimate, based on a meta-analysis of European studies, indicates that ADPKD prevalence is less than 5:10,000, i.e. it is a rare disease [33]. ADPKD is the fourth and fifth most common cause of ESRD in the USA [4] and UK [3], respectively. ADPKD may be clinically silent and it has been estimated that less than half of those affected are diagnosed during their lifetime [34]. Inheritance of *PKD1* mutations confers an earlier median age of onset of ESRD (54 years) than in those with *PKD2* mutations (74 years) [35]. Men tend to be more severely affected than women. Approximately 50% of individuals with ADPKD will require renal replacement therapy by 60 years of age [1, 36].

60.4 Genetics

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder and an important monogenic cause of hypertension [1, 37]. ADPKD is caused by germline mutations in either the *PKD1* gene (chromosome 16p13.3-p13.1) or *PKD2* gene (chromosome 4q21-q23). The *PKD1* and *PKD2* genes encode the proteins polycystin-1 and polycystin-2 [7, 8]. Mutations in *PKD1* and *PKD2* are responsible for ~80% and 15% of ADPKD cases, respectively [8, 38]. To date over 1500 unique mutations affecting the *PKD1* and *PKD2* genes have been characterised in various families (ADPKD Mutation Database ▶ http://pkdb.mayo.edu/). Mutations in the *PKD1* gene that are closer to the transcription start site (5′ end) potentially have a more severe effect on the translated polycystin-1 protein [39]. In general, mutations nearer the 5′ end of the gene are associated with a higher risk of intracranial haemorrhage compared to mutations closer to the 3′ end [40]. Since inheritance is autosomal dominant, there is a 50% chance of an affected child of either gender being born if a parent has ADPKD. This disorder has a very high penetrance (development of clinical disease in a genetically affected individual). A de novo mutation will be the cause in about 5% of those presenting with ADPKD, and up to 25% of affected individuals have no known family history of the condition [41]. Due to the large number of possible mutations within the genes and the difficulties inherent in assigning a causative role to some detected *PKD* gene sequence variants, confirmation by direct genetic sequencing of all individuals with the disorder remains challenging and furthermore, genetic testing may not be available in local clinical practice.

Of interest, even though all cells have a germline mutation, cysts only arise from a small percentage of tubular cells. It is believed that inheritance of a *PKD* mutation is a necessary but not sufficient factor for the PKD phenotype to manifest. One hypothesis is that a second somatic mutational 'hit' is needed on the 'normal' copy of the *PKD* gene before a cyst develops [42]. This could be another randomly occurring mutation in one of the *PKD* genes or a mutational 'hit' triggered by an environmental factor such as acute kidney injury [43]. Further somatic mutational events accumulate over time permitting the creation of multiple independent cellular clones that proliferate more rapidly and give rise to cysts (◘ Fig. 60.3a, b).

60.4.1 Genetic Testing

Careful attention to the ADPKD patient's family history can often provide a simple and reliable means of

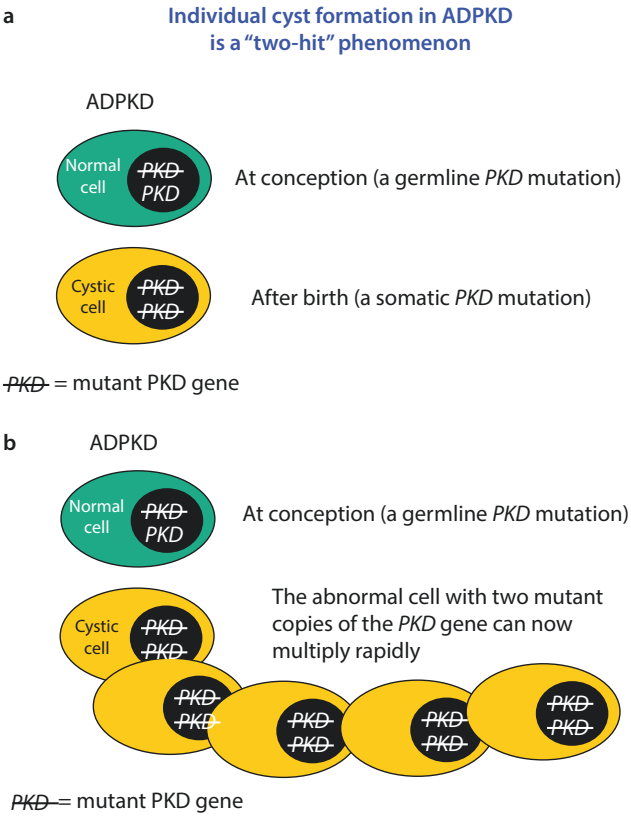

Fig. 60.3 Germline and somatic mutations of the *PKD* gene are required for kidney cyst formation. **a** Germline PKD mutation present at conception with subsequent somatic mutational event disrupting the 'normal' copy of the *PKD* gene. **b** The 'cystic' cell with mutations in both copies of the PKD gene has an altered phenotype. The 'cystic' cell has a growth advantage and proliferates resulting in the development of a kidney cyst

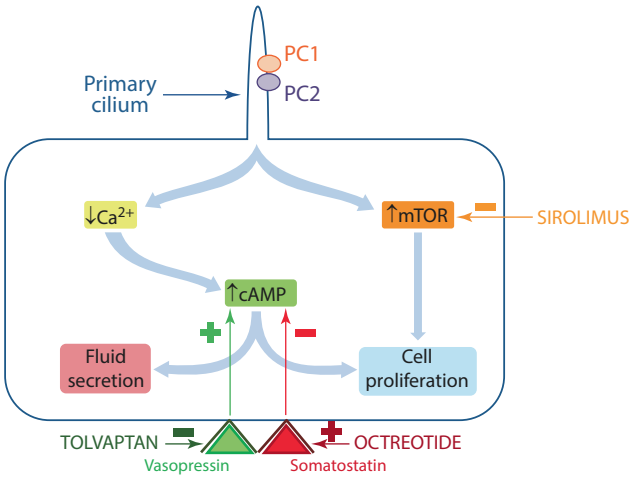

Fig. 60.4 Intracellular signalling disruption in ADPKD. Schematic of a renal tubular epithelial cell and its primary cilium. Mutations in the *PKD1* and *PKD2* genes lead to relative or absolute loss of function of the polycystin complex on the primary cilium. Reduced intracellular calcium influx occurs, and the compensatory increase in cAMP levels promotes fluid secretion and cell proliferation. Cell proliferation is also driven by upregulation of the mTOR pathway secondary to defective ciliary function. Vasopressin (antidiuretic hormone) acting through V2 receptors increases cAMP levels, while somatostatin inhibits cAMP generation. These main pathways are the targets of the therapeutic agents: sirolimus, tolvaptan, and octreotide. *cAMP* cyclic adenosine monophosphate, *mTOR* mammalian target of rapamycin, *PC1* polycystin-1, *PC2* polycystin-2

predicting the causative mutated gene (*PKD1* or *PKD2*). The family history of renal disease severity is predictive of the *PKD* mutation. A *PKD1* mutation is highly likely (positive predictive value 100%, sensitivity 72%) for patients with a family member with ADPKD who developed ESRD at <55 years of age. A *PKD2* mutation is predicted for a patient with at least one affected family member who continued to have sufficient renal function or developed ESRD when they were >70 years of age (positive predictive value 100%, sensitivity 74%) [44].

In practice there is clinical overlap between the phenotypes associated with *PKD1* and *PKD2* mutations, e.g. a patient with ESRD in their mid-60s may harbour either a *PKD1* or *PKD2* mutation. There can be extensive within-family variation in ADPKD with disease variability presumably reflecting the effects of other environmental, epigenetic, and genetic modifiers on disease progression. This variability in age-dependent clinical severity of ADPKD can make counselling individual family members very challenging.

Reliable genetic testing would provide a definite diagnosis in young adults or those individuals without a prior family history of ADPKD. Previously linkage-based diagnostic methods were used in large family pedigrees, but a direct mutation test is more practical. There are several unresolved technical challenges with the development of reliable and cost-effective mutation testing. These include the large size of the *PKD* genes and the multiple unique 'pathogenic' mutations identified already. Each allele (copy) of the *PKD* gene can have allelic heterogeneity that means both alleles must be screened. With the development of effective drug therapy for ADPKD, it has become more imperative to develop cost-effective molecular testing for this disease [38]. The next generation of DNA sequencing techniques will allow rapid analysis of individual patient's *PKD* genes and comparison of their sequence data with *PKD* mutation databases [45]. The UK Genetic Testing Network (► www.ukgtn.nhs.uk) does offer genetic testing for ADPKD. This genetics service may be particularly helpful when evaluating, as a potential living kidney donor, a young adult with a family history of ADPKD [46].

60.5 Pathophysiology

Abnormal function of the primary cilium of renal tubular cells appears to be an integral component of the pathophysiology of ADPKD that can be considered as one of the many ciliopathy disorders [47].

The primary cilium functions as a calcium-dependent mechanosensor, detecting urinary flow in the collecting tubules (◘ Fig. 60.4). The integral membrane-spanning proteins, polycystin-1 (PC1) and polycystin-2 (PC2), are located within the primary cilia of renal tubular epithelial cells [48]. The polycystins, together with other cilia proteins, regulate cell-cell interactions, epithelial proliferation, and downstream signalling events. PC2 interacts with PC1 and operates as a non-selective calcium channel. This calcium influx from the extracellular to the intracellular compartment triggers cell signalling in response to the flow-dependent movement (mechanosensing) of the primary cilium. The protein products of *PKD* genes, PC1 and PC2, inhibit cystogenesis. Inactivating mutations in *PKD1* and *PKD2* encoding the polycystins lead to the ADPKD phenotype [1, 7, 49].

Several interrelated mechanisms have been proposed to explain why cysts form and grow. Firstly, the ability of the primary cilium to sense urinary flow is compromised because polycystin protein structure or function is disturbed. This leads to reduced intracellular calcium levels resulting in compensatory increases in second messengers such as cyclic AMP (cAMP) and upregulation of mammalian target of rapamycin (mTOR), STAT3, Wnt, β-catenin, and MAPK pathways that mediate cell growth and proliferation [1, 7].

Secondly, there is a change in the polarity of tubular cells such that the normal orientation of the mitotic spindle, which would permit tubular elongation without dilatation, is rearranged permitting tubular dilatation and the possibility of cyst formation [50, 51].

Thirdly, within cyst walls, the epithelial cells proliferate consequent to the activation of several mitogenic pathways, and the end-point of this is an outpouching from the parent tubule. This outpouching is the beginning of a cyst, and once its diameter exceeds 2 mm, it will eventually lose communication with the glomerular filtrate and become a separate fluid-filled cyst.

Fourthly, the accumulation of fluid within the cyst is promoted by the effect of antidiuretic hormone (ADH) on the transepithelial secretion of chloride with sodium and water following into the cyst. Abnormal fluid secretion into cysts is associated with translocation of the sodium-potassium-ATPase pumps to luminal membranes (rather than being limited to the basolateral membranes) [48]. Cyclic AMP-dependent chloride channels, such as the cystic fibrosis transmembrane conductance regulator (CFTR), also contribute to cyst growth. The epithelial cells lining the cyst develop a 'secretory phenotype', and further fluid accumulation expands the cyst. Thus, pathways leading to increased intracellular cAMP levels, upregulated and disorganised cell proliferation, and fluid accumulation in cysts as a result of both the action of ADH and change to a secretory phenotype have become potential therapeutic targets [52].

The net result of these processes over time is that while only a small number of tubules will generate cysts, those that do give rise to cysts that continually release cytokines and growth factors that stimulate inflammation and fibrosis. As the cyst continues to expand, adjacent structures such as blood vessels, lymphatics, and tubules are physically disrupted or obstructed, and the cycle of inflammation, hypoxia, and worsening tubular injury with atrophy continues [53]. The remaining glomeruli hyperfilter, but eventually enough parenchyma will have been damaged that there is a steady, irreversible decline in GFR of between 4.4 and 5.9 ml/min per year with the potential for progression to ESRD [54].

Unlike the liver, where a synthetic and secretory function is usually normal despite multiple hepatic cysts, the kidney is dependent on the maintenance of a delicate balance between blood supply, lymphatic flow, and tubular architecture in order to function. Combined with the limited regenerative capacity of the kidney compared to the liver, the importance of trying to slow the progression of renal damage is readily appreciated.

60.6 Diagnosis

Ultrasound is the safest and most cost-effective imaging technique to establish a diagnosis of ADPKD. Molecular genotyping has been uncommon in clinical practice outside of defined research projects. If there is no prior family history of PKD, the diagnosis can be challenging particularly in younger adults who have been referred for assessment with relatively few cysts in each kidney. In adults, the presence of ten or more cysts in each kidney is generally considered diagnostic of ADPKD in the absence of renal or extra-renal features of rarer cystic kidney disorders such as tuberous sclerosis complex or von Hippel-Lindau syndrome.

Age-dependent ultrasound criteria for the diagnosis of ADPKD in families with *PKD1* mutation have been in use since the 1990s [55]. These specified that a diagnosis of ADPKD is established in individuals with a *PKD1* mutation family history if the following age-dependent cyst numbers are present: 15–30 years of age with at least two unilateral or bilateral cysts, 30–59 years of age with at least two cysts in each kidney, and >60 years of age with at least four cysts in each kidney. In practice, it is often uncertain whether an individual presenting with

Table 60.1 Ultrasound criteria for diagnosis of ADPKD in persons with a positive family history

Age (years)	*PKD1* genotype	*PKD2* genotype	Unknown genotype
15–29	≥3 cysts[a] (94.3%)	≥3 cysts[a] (69.5%)	≥3 cysts[a] (81.7%)
30–39	≥3 cysts[a] (96.6%)	≥3 cysts[a] (94.9%)	≥3 cysts[a] (95.5%)
40–59	≥2 cysts in each kidney (92.6%)	≥2 cysts in each kidney (88.8%)	≥2 cysts in each kidney (90%)
≥60	≥4 cysts in each kidney (100%)	≥4 cysts in each kidney (100%)	≥4 cysts in each kidney (100%)

Adapted from Pei et al. [56]
All criteria have a 100% positive predictive value
[a]Unilateral or bilateral cysts

cystic kidneys has a family history of ADPKD secondary to a *PKD1* or *PKD2* mutation.

Revised age-dependent criteria for the diagnosis of ADPKD in families of unknown genotype were published in 2009 [56]. A diagnosis of ADPKD is established as follows: the presence of three or more cysts (unilateral or bilateral) in individuals 15–39 years of age, two or more cysts in each kidney in individuals 40–59 years of age, and four or more cysts in each kidney in persons >60 years of age (Table 60.1). If a family member is being considered as a potential living kidney donor, then the diagnosis of PKD is excluded if there are two or fewer cysts in individuals >40 years of age (despite the personal history of ADPKD). A diagnosis of ADPKD is almost certainly excluded when renal cysts are absent in individuals 30–39 years of age (false-negative rate 0.7%) [56]. One important caveat is that these criteria were developed using images from ultrasound scanners capable of detecting cysts >1 cm in diameter. Modern high-resolution ultrasound scanners can detect kidney cysts with diameters 2–3 mm [57].

60.6.1 ADPKD Diagnosis When Genotype Is Unknown

Up to 10–25% of individuals may be referred for assessment of ADPKD (e.g. multiple kidney cysts are present) but have no other family members known to be affected. Using ultrasound for the diagnosis of ADPKD is not sufficient because the age-dependent criteria were developed in individuals who had a 50% risk of ADPKD [55, 56]. In individuals with a negative family history, there is no definitive number of cysts that confirms a diagnosis of ADPKD. The presence of 10 or more cysts in each kidney makes the ADPKD more likely particularly if the kidneys are enlarged and liver cysts are present [57].

Genetic testing should be considered to confirm the diagnosis of ADPKD, especially if only a few cysts are present, with the proviso that genetic testing is not yet freely available and remains technically challenging partly because of the complex DNA sequence of the larger PKD1 gene and the growing number of pathogenic mutations within the PKD databases.

60.7 Differential Diagnosis

Multiple kidney cysts occurring at a young age, presence of developmental malformations, or the early onset of gout or type 2 diabetes should prompt consideration of alternative diagnoses to ADPKD and discussion with a clinical geneticist. Rarely individuals may have a deletion of both *PKD1* and the adjacent *TSC2* gene on chromosome 16p and express the tuberous sclerosis phenotype in addition to having a much earlier onset of ADPKD in infancy [58]. Others who possess mutations in both *PKD1* and *PKD2* also display more severe disease. The main differential diagnoses for ADPKD are listed in Table 60.2.

60.8 Treatment of Polycystic Kidney Disease

60.8.1 General Principles

Identification and treatment of hypertension, dietary salt restriction, avoiding excess dietary protein intake, early introduction of statin treatment, and efforts to correct disorders of bone mineral metabolism may all help to reduce the progression of ADPKD and decrease cardiovascular morbidity.

As the progression of ADPKD is driven in part by vasopressin (antidiuretic hormone), it is logical to advise affected individuals to stay well hydrated (to reduce antidiuretic hormone release). This strategy of maintaining a high oral fluid intake may be beneficial in the long-term management of ADPKD and is being studied in several clinical trials [1, 10].

Prompt treatment of cyst infections is most effective with lipid-soluble antibiotics that have better tissue penetration, e.g. ciprofloxacin or sulfamethoxazole-trimethoprim. Haematuria may be secondary to cyst rupture, but it is important to consider other diagnoses that may result in renal tract bleeding including nephrolithiasis and urological malignancy.

Table 60.2 Renal cystic disorders

Cystic kidney disorders			
Cystic kidney disease (*and mode of inheritance*)	**Incidence**	**Clinical features distinguishing from ADPKD**	**Comments**
Acquired cystic disease of the kidney (*not inherited*)	5–20% incident dialysis patients; up to 80–100% after 10 years on dialysis	Cysts develop as a consequence of ESRD due to other causes than ADPKD. Cysts within small or normal-sized kidneys	Cysts have premalignant potential (unlike those of PKD). New onset of haematuria in a dialysis patient should trigger the investigation for renal tract neoplasms
Tuberous sclerosis complex (AD)	1:6000	Characteristic skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, Shagreen patches); CND involvement (hamartomas astrocytoma): retinal hamartomas, developmental delay, epilepsy	Multiple renal cysts with benign angiomyolipomas that may harbour RCC. Mutations in *TSC1* and *TSC2* genes
Autosomal recessive polycystic kidney disease (AR)	1:20,000	Diagnosis in utero or infancy; Potter's phenotype; hepatic fibrosis, portal hypertension	Gene defect in *PKHD1* encoding polyductin May require liver and kidney transplantation
Von Hippel-Lindau disease (AD)	1:36,000	Retinal angiomas, cerebellar and spinal haemangioblastoma, renal tumours and phaeochomocytoma	Mutations in *VHL* gene associated with the development of RCC
Nephronophthisis (AR)	1:50,000–1:100,000	Retinal dystrophy, blindness, oculomotor apraxia, developmental delay (10% cases); kidneys often of normal size or small	Commonest genetic cause of renal failure in children. Multiple pathogenic mutations identified
Medullary cystic kidney disease (AD)	1:100,000	Hyperuricaemia, gout, medullary cysts	Serum creatinine often elevated prior to the later appearance of cysts. Associated with *UMOD* gene mutations
Polycystic liver disease (AD)	Unknown	Minor, if any, renal cystic involvement	Mutations in *PRKCSH* or *SEC63* genes
Renal cysts and diabetes syndrome MODY5 (AD)	Unknown	Renal cysts and diabetes syndrome. Pancreatic atrophy. May be associated with other structural genitourinary malformations	Mutations in *HNF1B* gene. Part of the maturity-onset diabetes of the young (MODY) spectrum
Birt-Hogg-Dubé syndrome (AD)	1:200,000	Presence of fibrofolliculomas on face and trunk	Mutation in gene encoding folliculin. May have recurrent pneumothoraces; associated with rare renal tumours

AD autosomal dominant, *AR* autosomal recessive, *CNS* central nervous system, *ESRD* end-stage renal disease, *RCC* renal cell carcinoma

60.8.2 Hypertension

The development of hypertension is almost universal in ADPKD and is typically present when the kidneys have increased in size but before renal failure is present. Loss of normal nocturnal dipping in blood pressure usually occurs before the emergence of more sustained hypertension. Antihypertensive treatment reduces the risk of hypertension-related complications in chronic kidney disease, but lowering blood pressure has not convincingly been demonstrated to retard the progression of ADPKD [59]. Hypertension will respond to renin-angiotensin axis blockade with ACE inhibitors or angiotensin receptor blockers (ARBs) [60]. The use of diuretics should be avoided because of the evidence that cyst growth is mediated by vasopressin (antidiuretic

hormone). In theory, diuretic-induced intravascular volume depletion could accelerate cyst growth by increasing vasopressin levels.

60.8.3 Preparing for Renal Replacement Therapy

ADPKD is typically slowly progressive with a predictable individual rate of GFR decline. This allows for advanced planning for renal replacement therapy (RRT) [29]. The median age of ESRD onset for persons with the more prevalent *PKD1* gene defect is 54 years of age [61]. One of the advantages of prolonged follow-up of persons with ADPKD at nephrology clinics is the ability to plan the choice of RRT and optimal timing of RRT start.

Options for RRT include pre-emptive kidney transplant (living donor or listing for deceased donor transplant), haemodialysis, or peritoneal dialysis. Outcomes for persons with ADPKD who are successfully transplanted are generally more favourable than for any other common causes of ESRD such as diabetes or glomerulonephritis. There is obviously no risk of recurrent disease in the renal allograft.

60.8.4 Practical Implications for Renal Replacement Therapy in Persons with ADPKD

The *physical size of polycystic kidneys* may be a significant clinical issue when planning for pre-emptive transplantation. Accurate measurement of kidney size, employing MRI, or CT scanning, will allow the volume of each kidney to be assessed. Further discussion with the transplant surgery team is necessary to establish if there will be sufficient room in the pelvis for surgical placement of a transplanted kidney (Fig. 60.5). If not, then the patient will need counselling on the requirement for polycystic kidney nephrectomy and the attendant risks of this procedure. Surgeons may elect to perform a bilateral nephrectomy to ensure adequate space for transplant in either the left or the right iliac fossa. Either open or laparoscopic nephrectomy are surgical options.

Other *indications for nephrectomy* include recurrent kidney cyst infections, staghorn calculi, persistent severe cyst pain, or recurrent visible haematuria resulting in anaemia. The risk of kidney cancer is not increased in persons with polycystic kidney disease, but the diagnosis of cancer is challenging since symptoms of loin pain and visible haematuria are common and often reasonably attributed to ADPKD itself. Imaging of the kidneys to identify malignancy is also problematic since multiple simple and complex cysts already grossly distort the renal anatomy. Occasionally an incidental renal cell carcinoma is found on careful sectioning of a polycystic kidney following nephrectomy. The finding of an incidental cancer will mean delaying transplantation until further cancer workup is completed and a disease-free interval is recorded.

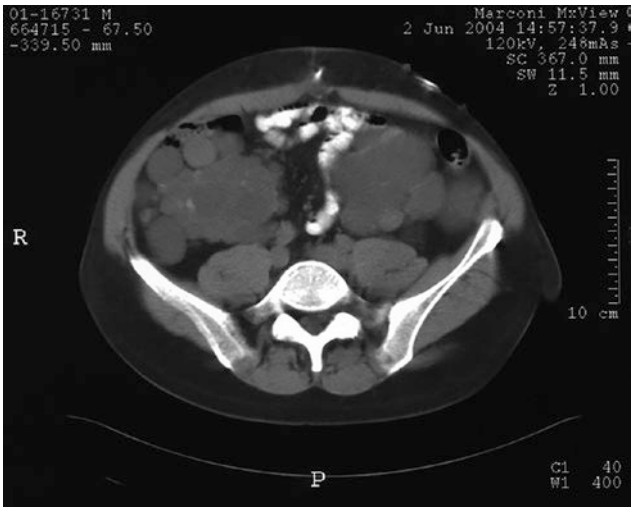

Fig. 60.5 CT scan of the pelvis. Massively enlarged polycystic kidneys extend into the pelvis. Bilateral nephrectomy was subsequently undertaken to enable this patient to have a successful renal transplant procedure

Bilateral nephrectomy in ADPKD is a major procedure with considerable post-operative morbidity, and patients need to be advised concerning chest, wound, and retroperitoneal infections and the potential requirement for blood transfusion (with risk of HLA sensitisation) in the perioperative period. As the patient is anuric, they are rendered dialysis dependent, and only haemodialysis support is suitable in the post-op period. In view of these considerations, it is generally advisable to have established reliable vascular access, preferably by creating an arteriovenous fistula, prior to proceeding to nephrectomy. If a fistula has been fashioned, it may be several months before it is mature enough to be usable as vascular access. In the absence of a fistula (or arteriovenous graft), a tunnelled jugular vein catheter may be placed preoperatively. Haemodialysis support immediately post-bilateral nephrectomy can be complicated by difficulties establishing an accurate dry weight. It is important to account for the weight loss related to both the removal of the large kidneys (as much as 6–8 kg) and the loss of intravascular volume if there is continued oozing of tissue fluid from the retroperitoneal site of operation into a 'third space'. Post-operative ileus with intraluminal accumulation of fluid may also occur due to intraoperative bowel mobilisation.

Recovery from bilateral nephrectomy may take several months; therefore, in planning an elective living donor transplant procedure, it is generally prudent to wait for at least 3–6 months after nephrectomy before proceeding to transplantation.

The physical size of polycystic kidneys also has practical implications for the placement of a *peritoneal dialysis* catheter and subsequent effective peritoneal dialysis therapy. Enlarged kidneys may make it difficult to ensure appropriate placement of the catheter tip in the pelvis and increase the likelihood of migration of the catheter within the abdomen. Larger volumes of peritoneal dialysate in CAPD or APD regimens are also more likely to cause patient discomfort. The addition of peritoneal dialysate fluid can exacerbate the predisposition to abdominal herniae (which are more common in persons with ADPKD). Cyst pain and cyst infection in polycystic kidneys may mimic symptoms and signs of peritonitis and can lead to diagnostic dilemmas if peritoneal dialysate effluent cultures are negative. Rupture of a kidney cyst can occasionally lead to visible blood staining of peritoneal fluid. Although this is an alarming symptom for patients to experience, it is usually self-limiting and settles without need for intervention. Despite these potential complications, many patients will be able to tolerate peritoneal dialysis.

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60.8.5 Assessment of a Potential Living-Related Kidney Donor When There Is a Family History of ADPKD

Adult offspring of an affected parent may be considered as potential living related kidney donors [62, 63]. All potential donors should be counselled about the possibility of an ADPKD diagnosis being established before embarking on assessment [62]. Typically, the affected parent will have a *PKD1* mutation, i.e. median age of onset of ESRD in their 50s. All potential living kidney donors will have detailed kidney imaging as part of their extended clinical assessment. A CT scan or MRI (undertaken to identify the number and calibre of kidney blood vessels) will also be able to exclude ADPKD in potential adult donors. There are published criteria for the diagnosis or exclusion of ADPKD using CT or MRI with >10 cysts confirming the diagnosis and <10 cysts excluding the disease [57]. For persons 40 years or older, with a first-degree relative with ADPKD, the finding of normal kidneys rules out ADPKD in the potential donor. Many transplant centres would still be reluctant to use a kidney from a younger relative under 30 years without first undertaking mutation screening of the first-degree relative with ADPKD and their potential living kidney donor. This may still not answer the question because up to 15% of persons with ADPKD will not have an identified pathogenic mutation following genetic screening [63].

60.9 Novel Therapies for ADPKD

Research to understand the cell biology of cyst growth coupled with studies using animal models of polycystic kidneys has been critical to the development of new drug treatments for ADPKD (■ Fig. 60.4). Cyst growth can be slowed by blocking the cell membrane transporters that increase fluid secretion into cysts [1, 7, 48]. In vivo data demonstrated that blocking vasopressin V2 receptor would lower renal tubular epithelial cyclic AMP levels. V2 receptor blockade slowed the progression of renal disease in animal models of polycystic kidneys [1, 7]. Randomised controlled clinical trials of tolvaptan, a V2 receptor antagonist, demonstrated long-term efficacy measured by serial measurements of renal function and polycystic kidney volume by MRI scans [64–66]. In the UK, tolvaptan (a vasopressin antagonist) became the first NICE-approved treatment to slow the progression of cyst development and progression of renal failure in ADPKD. Tolvaptan can be prescribed for patients with ADPKD and CKD stages 2 or 3 with rapidly declining GFR. The main side effects of tolvaptan are thirst and polyuria. In the clinical trials of tolvaptan, liver function test (LFT) abnormalities were more common than placebo therefore monthly LFT monitoring is mandatory for the first 18 months of treatment.

Other clinical trials of drugs for ADPKD have been completed or are in progress. Therapeutic agents being studied include mTOR inhibitors, metformin, statins, tyrosine kinase inhibitors, and somatostatin analogues [1, 10, 67]. Continued research focused on the biology of ADPKD should ultimately translate into safe and cost-effective treatments that significantly extend renal survival.

60.10 Resources and Patient Information

- PKD charity ► https://www.pkdcharity.co.uk
- NHS Health A-Z: Polycystic Kidney Disease ► https://www.nhs.uk/conditions/autosomal-dominant-polycystic-kidney-disease-adpkd/
- Kidney Care UK: Polycystic Kidney Disease ► https://www.kidneycareuk.org/about-kidney-health/conditions/polycystic-kidney-disease-pkd/

Chapter Review Questions

1. For persons with ADPKD, why are diuretic drugs avoided (if possible) in treatment of hypertension?
2. What problems can be caused by very large polycystic kidneys?
3. Adult children of an affected parent with ESRD secondary to ADPKD are being considered as a potential living-related kidney donor. What kidney imaging is best to exclude ADPKD in the potential donors?
4. Tolvaptan (a vasopressin antagonist) is licensed for use in ADPKD to reduce the rate of cyst growth and slow the progression of renal failure. What issues are relevant in clinical practice?

Answers

1. Diuretics can trigger intravascular volume depletion and result in a rise in vasopressin (antidiuretic hormone) levels. Vasopressin stimulates the growth of cysts in ADPKD. Diuretics may accelerate cyst development resulting in more rapid progression of ADPKD.
2. Very large polycystic kidneys may extend into the pelvis limiting the space available for a kidney transplant. The surgical team may recommend a nephrectomy before the patient is listed for transplantation. Large polycystic kidneys may also interfere with the placement of a peritoneal dialysis catheter and limit the effectiveness of peritoneal dialysis exchanges.
3. An MRI or CT scan is helpful in determining is a first-degree relative is affected by ADPKD. A normal scan in a person >40 years of age rules out ADPKD in the potential donor. Many transplant centres are still reluctant to use a kidney from a younger donor <30 years of age without also undertaking gene mutation screening.
4. Tolvaptan blocks the action of vasopressin leading to troublesome symptoms of polyuria and thirst. Starting with the lowest recommended dose (45 mg morning and 15 mg evening) and allowing the person with ADPKD to get used to the symptoms is helpful before increasing to higher and more effective doses. In clinical trials, there was a higher incidence of liver function test abnormalities in patients treated with tolvaptan compared to placebo. Monitoring liver function tests every month for 18 months and then every 3 months is recommended best practice.

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