Some genetic mutations lead to cystic changes in the kidney (table). In contrast to the recessive forms (1–3), autosomal dominant polycystic kidney disease (ADPKD) with an incidence of 1 : 500 to 1 : 1000 is one of the commonest hereditary diseases (4). Some 5 million people worldwide are affected. In many countries ADPKD is the fourth most frequent cause of end-stage renal failure.

About 85% of these diseases are caused by mutations in the PKD1 gene, the remaining 15% are due to PKD2 mutations. On average, one half of the children inherit the mutated gene from their parents and one half of all mutation carriers develop progressive renal insufficiency. Following the onset of disease between the ages of 30 and 50 years, end-stage renal failure is usually reached between the age of 50 and 60 years. At this point the kidneys are massively enlarged and completely interspersed with cysts (figure 1).

The initial manifestations and early complications include

- Micro- or macrohematuria (50%)
- Moderate proteinuria (< 1 g/day)
- Recurrent cyst infections
- Arterial hypertension (although 30 to 60% of patients then still have a normal glomerular filtration rate [GFR])
- Abdominal/flank pain due to compression effects (60%)
- Moderate polyuria (box 1).

There is no increased incidence of renal cell tumors. If they do occur, however, they may often be expected to be bilateral and multifocal.

Methods
Based on a selective review of the current literature, the symptomatology of ADPKD is described and new findings relating to the pathophysiology and potential therapeutic approaches are presented.

Progression
Progression of ADPKD may differ greatly between individuals and although different risk factors have been identified, the course is difficult to predict from one case to another. The
incidence of end-stage renal failure increases with age. Genetic factors play an important role. For example, patients with a PKD2 mutation have a mild course, with end-stage renal failure often not occurring until after the age of 70 years. In the early stage of the disease the growth of the renal cysts does not impair renal function. Renal function compromise begins from a kidney size of 1000 ml onwards. From a kidney volume of > 1500 ml, a mean decrease in glomerular filtration rate (GFR) of around 4 to 5 ml/min/year is to be expected. In patients with a kidney volume of > 750 ml the kidneys grow in size by > 5% per year (5).

**Extrarenal manifestations**

**Aneurysms**

ADPKD is a systemic disease (box 1). With a prevalence of 4 to 6%, especially cerebral aneurysms contribute considerably to mortality (about 5%) by causing subarachnoid hemorrhages. An increased incidence of aneurysms is particularly associated with a positive family history. It is therefore advisable to perform magnetic resonance angiography in
patients with a positive family history, suspicious symptoms such as new onset headaches, or a high-risk occupation such as airline pilot (box 2).

Screening of all patients is not generally recommended because the risks of potential therapy are considerable. Even at specialized centers, the rate of serious complications is 8 to 12% (6). On the other hand, the mortality and the rate of serious neurological complications following aneurysmatic hemorrhages is more than 50% (7), which means that a risk-benefit analysis is not easy in individual cases.

Aneurysms generally rupture when they reach a size of about 10 mm (6). Most centers recommend intervention at a size of 5 mm or more. As an alternative to surgical intervention, the coiling procedure is now increasingly used (serious complications 3 to 5%, mortality 1 to 2%) (e1). Aneurysms of the aorta occur as frequently as cerebral aneurysms. They can be overlooked in ultrasound scans if they are completely obscured by the cystic kidneys. The ruptures of these aneurysms probably also contribute significantly to these patients’ mortality (e2).

**BOX 1**

**Renal and extrarenal manifestations of autosomal dominant polycystic kidney disease**

**Renal**
- Micro- or macrohematuria (50%)
- Proteinuria (< 1 g/day)
- Recurrent cyst infections
- Arterial hypertension (> 80%, 30–60% with normal renal function)
- Abdominal/flank pain (60%)
- Nephrolithiasis (20–30%)
- Moderate polyuria

**Extrarenal**
- Liver cysts
- Pancreatic cysts
- Cerebral aneurysms
- Heart valve abnormalities
- Aortic aneurysms
Other extrarenal manifestations
Occasionally heart valve abnormalities develop, with mitral valve prolapse (26%) and mitral valve insufficiency (13%) being the most common (e3). Colonic diverticula are a frequent concomitant of ADPKD and often only become apparent as diverticulitis after a renal transplantation (e4). Besides renal cysts, liver and pancreatic cysts are common findings. Liver failure is rare. However, due to the compression they exert on other organs, massively enlarged liver cysts can cause severe symptoms such as abdominal pain, loss of appetite and cachexia. This complication is seen especially in women (e5). Occasionally, partial liver resection or liver transplantation is indicated in these cases (e6). Cystic changes may also occur in the bile ducts and manifest as cholangitis.

Renal complications
Arterial hypertension
Arterial hypertension is detectable in more than 80% of all patients. About 30 to 60% of these patients still have completely normal renal function at diagnosis. However, hypertension is one of the most important factors for progression (8). Unfortunately, neither the optimal target blood pressure nor the ideal antihypertensive agent have been adequately established by clinical studies. Because of the cardiovascular effects, preference is given to angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). A randomized study (HALT, "Progression of Polycystic Kidney Disease") is now being conducted in about 1000 patients in the USA to determine whether combination therapy of ACEI plus ARB offers an advantage compared to ACEI monotherapy. Independently of the optimal pharmacotherapy, ADPKD patients should maintain a low sodium diet (e7).

Cyst infections
The infection of individual cysts is one of the frequent complications of ADPKD. Since the cysts usually have no connection with the lower urinary tract, cyst infections may be associated with the finding of sterile urine. As in typical urinary tract infections, E. coli and other gram negative organisms are among the commonest etiological agents. Some antibiotics, especially aminoglycosides, however, penetrate poorly into cysts and fail to reach sufficient concentrations in cyst fluid (9). Quinolones are preferred in clinical practice since they have been reported to have good cyst penetration. The treatment of recurrent infections or infections that cannot be controlled by conservative strategies is difficult. In many cases, infected cysts are difficult to localize radiologically, with the result that nephrectomy is occasionally necessary. Nephrolithiasis develops in 20 to 30% of ADPKD patients. The often slight concentrating deficit and polyuria, on the other hand, are of secondary clinical significance.

Refractory pain
Chronic abdominal pain caused by cyst expansion, rupture or infection is common (10, e8). It is important, however, to rule out nephrolithiasis, an abdominal aortic aneurysm or renal cell cancer. Opiates should be used only for limited periods because of their addictive potential, while nonsteroidal anti-inflammatory agents can impair renal function. The ablation of individual cysts is subject to complications and should only be performed if the anticipated benefits clearly outweigh the potential risks. One new approach is laparoscopic cyst decortication (e9).

Diagnosis and differential diagnosis
The diagnosis of ADPKD is usually based on clinical findings. Typical features include
- Age between 30 and 50 years
- Positive family history (approx. 70%)
- Markedly enlarged kidneys on both sides with multiple, irregularly arranged cysts
- Renal function compromise, often only slight at diagnosis.

Especially the detection of liver cysts or evidence of other extrarenal manifestations are useful in making the diagnosis in patients with a negative family history (approx. 30%). In high-risk patients, such as children of ADPKD patients, the diagnosis can be made by ultrasonography in patients aged 20 years and older if at least 2 renal cysts (bilateral) are
detectable. In contrast, the absence of cysts rules out the presence of disease in individuals over 30 years of age (11).

The relatively high percentage of negative family histories is explained by a high spontaneous mutation rate, incorrect fatherhood data and faulty diagnosis – such as premature death from aneurysmatic hemorrhage. A genetic diagnosis (cost around 4000 euros) is only necessary in exceptional cases, but can provide a predictive diagnosis in relatives. The size and complexity of the PKD1 gene allows the detection of mutations by DHPLC (denaturing high performance liquid chromatography) in 65 to 70% and with direct sequencing in about 85% of cases (e10, 11). Since a conclusive genetic diagnosis in many cases has far-reaching consequences and sometimes disadvantages for patients, the advisability of making this diagnosis should be closely considered and discussed with the patient. If ongoing clinical studies show that therapeutic measures delay the progression of the disease, early genetic diagnosis may be indicated. Predictive diagnostics should only be carried out after thorough genetic counseling.

**BOX 2**

**Indication for MRI angiography of cerebral vessels**

- Positive familial history of cerebral aneurysms (e.g. unexplained cause of sudden death at a relatively young age)
- Patients after rupture of cerebral aneurysms
- Elective operations with possible hemodynamic instability
- High-risk occupations
- Patient’s wish

The incidence of cerebral aneurysms is about 16% in patients with a positive familial history (the prevalence in the normal population is 1–5% in autopsy studies). In patients without a familial history, the rate of aneurysms is 6%; these are generally small (1–7 mm) and rarely rupture, and therefore general screening of patients is not recommended (e27).

**DIAGRAM 1**

“Two-hit hypothesis” of cystogenesis. ADPKD patients have one healthy and one mutated allele per cell. The heterozygotic state results in a normal tubule geometry. In one individual cell there is somatic inactivation of the second allele (second “hit”). This cell loses the proliferation inhibition and forms the point of origin of a new cyst. ADPKD, autosomal dominant polycystic kidney disease.
Von Hippel-Lindau’s syndrome
Autosomal dominant inherited Von Hippel-Lindau’s (VHL) syndrome is characterized by a combination of hemangioblastomas – especially in the retina and cerebellum –, renal cell cancers and the occasional presence of pheochromocytomas (12). In the early stage, precancerous renal cysts may occur which result in enlargement of the kidneys and may be deceptively similar to ADPKD. On the other hand, renal function impairment is not observed in VHL syndrome. The most reliable guide is the family history, which often includes tumors at an early age, although spontaneous mutations also occur.

Tuberous sclerosis
Autosomal dominant tuberous sclerosis occurs with an incidence of 1 : 5000 to 10 000 and is caused by mutations of the TSC1 or TSC2 gene (13). Especially mutations of TSC2, which is located directly beside the PKD1 gene on chromosome 16, result in polycystic renal changes resembling ADPKD. Angiomyolipomas of the kidneys, angiofibromas, retinal hamartomas and benign neurocutaneous tumors allow differentiation.

Autosomal recessive polycystic kidney disease
Autosomal recessive polycystic kidney disease (ARPKD) is based on a mutation in the PKHD1 gene. Usually it already manifests perinatally and is characterized not only by hyperechoic kidneys with occasional cortical cysts but also by pulmonary hypoplasia and portal fibrosis (1). In individual cases, the diagnosis is not made until late adolescence (e12).

Nephronophthisis
Mutations in 6 different genes (NPHP1 to NPHP6) cause an autosomal recessive disease characterized by the formation of cysts at the corticomedullary junction without conspicuous enlargement of the kidneys, and generally leads to end-stage renal failure before the age of 20 years (1, 14). Characteristically, numerous extrarenal manifestations are seen such as retinitis pigmentosa, cerebellar ataxia, oculomotor apraxia and hepatomegaly (table).

Medullary cystic kidney disease
Autosomal dominant medullary cystic kidney disease (MCKD) is caused by mutations of MCKD1 or MCKD2 (Tamm-Horsfall protein); the gene mutation on chromosome 1q21 underlying MCKD1 is so far unknown. Since end-stage renal failure occurs between the ages of 30 and 60 years, this disease is often difficult to distinguish from ADPKD. With an incidence of < 1 : 10 000, however, it is much more rare (14).
Pathogenesis

Genetics
In 1995 and 1996 the first two genes were cloned whose mutations are responsible for > 95% of all ADPKD diseases (15, 16). PKD1 and PKD2 are localized on chromosomes 16 and 4 and code for the two proteins polycystin-1 and polycystin-2. Polycystin-1 is a large, membrane anchored protein with about 4302 amino acids (14, 15, e13). Its exact function is unknown. Polycystin-1 interacts with polycystin-2 (e15, 16). Polycystin-2 is a calcium permeable ion channel of the TRP family (16) and is localized both on the plasma membrane and in the endoplasmic reticulum (ER). In the ER it promotes depletion of the ER calcium stores after stimulation by receptors in the plasma membrane (e17).

PKD1/PKD2 knockout mice
Deletion experiments (knockout) in mice have demonstrated the importance of PKD1 and PKD2 in the pathogenesis of ADPKD (17, 18, e18–21). Interestingly, however, only homozygotic animals developed the disease, while heterozygotic animals showed a relatively unremarkable course (e18). This contradiction in relation to human disease is explained by the "two hit theory" (18, 19) according to which – as in tumor suppressor genes – initially a germline mutation is inherited from one parent (diagram 1). Only the tubular cells in which a second, somatic mutation occurs, have cyst formation potential. This theory may explain why only about 1% of all nephrons are affected by cysts.

Ciliary hypothesis of cystogenesis
Almost all mammalian cells have cilia. The ciliary hypothesis (20) originated more than 10 years ago with the analysis of the cystic orpk mouse (Oak Ridge Polycystic Kidney Mouse). This mouse model bears a mutation in an essential ciliary protein (21). Fluid flow induced deflection of the primary cilium leads to an increase in the intracellular calcium concentration of tubule cells (22, e22) (diagram 2). This increase in calcium is absent in the presence of mutations of polycystin-1 or inhibition of polycystin-2 function (e23). The polycystin complex is assumed to form a mechanosensor which is activated by ciliary movement. Which cellular programs are activated by this mechanism, however, remains obscure. Initial findings suggest that the cilium is important for the spatial arrangement of the tubular epithelial cell.
Therapy of PKD in animal models

Cystic cells secrete fluid. The secretion is stimulated by an increase in the intracellular cAMP concentration. One component of the cystic fluid is antidiuretic hormone (ADH) which via the vasopressin-2 receptor contributes to the cAMP elevation. Vasopressin-2 receptor antagonists have been shown to inhibit cyst growth in various animal models and to favorably influence renal function (23, e24). A similarly positive effect has also been demonstrated for an immunosuppressive drug from transplantation medicine, the mTOR inhibitor rapamycin (mTOR = mammalian target of rapamycin) (24, e25): it was shown in 3 different PKD models that rapamycin therapy can drastically inhibit cystic growth. mTOR kinase is part of two multiprotein complexes, mTORC1 and -2, the former being inhibited by rapamycin (diagram 3) (e26). mTORC1 is inhibited by the TSC1/TSC2 complex. Mutations of TSC1 or TSC2 lead to tuberous sclerosis (TSC), which is associated with polycystic renal changes especially in TSC2 mutations. Recent data show that polycystin-1 interacts with mTOR and tuberin, the product of the TSC2 gene (25). Its function, in combination with tuberin, could be to inhibit mTORC1. mTOR does in fact appear to be markedly upregulated in cystic epithelial cells, which represents a rational basis for pharmacological intervention with rapamycin. The mechanism of action of rapamycin is explained by the fact that it induces apoptosis of cystic cells. Since rapamycin is effective in various animal models, it may be assumed that TSC/mTOR is also implicated in other forms of polycystic kidney disease (figure 2). Interestingly, in a statistically non-meaningful number of transplanted patients treated with rapamycin (n = 4) a decrease in intrinsic kidney volume was observed which was markedly above that seen in ADPKD patients without rapamycin (25).

Clinical studies

At present altogether 7 ongoing pharmacological intervention studies are registered under the code “ADPKD” with the National Institutes of Health (NIH; http://clinicaltrials.gov/), 2 of them in German speaking countries.

An initial clinical study with mTOR inhibitors was launched in Germany and Austria at the end of 2006. This study will enroll a total of 400 patients. The patients will receive either placebo or everolimus on a double-blind basis; it will be attempted to achieve a trough level
of 3 to 8 ng/ml as targeted after renal transplantation. Patients with pre-existing impairment of renal function (GFR 30 to 89 ml/min) or markedly enlarged kidneys (=1000 ml) aged between 18 and 65 years can participate in this study if they have had no previous severe infections or aneurysmatic hemorrhage. The primary endpoint of this study is the enlargement in kidney volume after 24 months measured by magnetic resonance imaging (MRI). The secondary endpoints are the change in renal function, incidence of end-stage renal failure, changes in blood pressure and tolerability of the study medication.

A second Swiss study is investigating the influence of sirolimus on the kidney volume of ADPKD patients. The study is unblinded and will follow 100 patients with a glomerular filtration rate of more than 70 ml/min for 2 years. Further studies are evaluating the effect of somatostatin analogs (Italy and USA) and double blockade of the renin-angiotensin system (NIDDK, USA).

**Prospects**

ADPKD is the commonest symptomatic monogenically heritable disease. It is still untreatable and leads to end-stage renal failure in half of those affected. In the last 3 years, successful therapeutic approaches have been evaluated in animal models of ADPKD and are currently under investigation in controlled therapeutic trials in patients. This development raises hopes that specific therapies are now moving within reach.

**Conflict of Interest Statement**

Dr. Kühn has received lecture fees from Novartis. Prof. Walz is the Principal Investigator (PI) of the study on the efficacy of certican in ADPKD being conducted by Novartis and acts as a consultant to Novartis.

**REFERENCES**

For e-references please refer to the additional references listed below.

ADDITIONAL REFERENCES


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