Summary

Autosomal dominant polycystic kidney disease is an inherited systemic disorder with major renal manifestations and, in some cases, abnormalities in the liver, the pancreas, the brain, the arterial blood vessels, or a combination of these sites.

The disease affects approximately 300,000 to 600,000 Americans of either sex, and without racial predilection. Each child of an affected parent has a 50% chance of inheriting the mutated gene, which is completely penetrant. Autosomal dominant polycystic kidney disease arises as a spontaneous mutation in approximately 5% of cases. However, in about one fourth of newly diagnosed cases, patients report no history of the disease, indicating that many familial cases go undetected.

Autosomal dominant polycystic kidney disease begins in utero, but signs of the disease may not be detected for several decades. Autosomal dominant polycystic kidney disease is caused by mutations in either of the two genes encoding plasma membrane-spanning polycystin 1 and polycystin 2 (PKD1 and PKD2), respectively. The polycystins regulate tubular and vascular development in the kidneys and other organs (liver, brain, heart, and pancreas), and interact to increase the flow of calcium through a cation channel formed in plasma membranes by polycystin 2. A mutation of either polycystin can disrupt the function of the other, resulting in similar clinical

presentations. However, mutations of PKD1 are more common than mutations of PKD2 (accounting for 85% of cases), are likely to be associated with more renal cysts, and lead to renal insufficiency on average 20 years earlier (median ages at the time of death or end-stage failure, 53 and69 years, respectively).

In adults with a positive family history, the diagnosis of autosomal dominant polycystic kidney disease is established by radiologic evidence of bilateral, fluid-filled renal cysts. Ultrasonography reliably detects cysts that are 1 cm or larger in diameter and is highly sensitive for the diagnosis in adults.

Autosomal dominant polycystic kidney disease can be caused by hundreds of different intragenic PKD1 and PKD2 mutations. Since current genotype testing can identify only approximately 70% of the known pathogenic mutations, it is not a useful screening tool.

Current treatment is directed towards reducing morbidity and mortality due to the complications of the disease. It included treatment of hypertension, pain, cyst hemorrhage, cyst infection, nephroplithiasis.

Patients with autosomal dominant PKD do better on dialysis than do patients with other causes of ESRD, while renal transplantation is the treatment of choice for ESRD in autosomal dominant PKD.

Vasopressin, Somatostatin and other drugs shown to be effective in preclinical trials and of potential value for the treatment of human PKD, these drugs, which have been developed for the treatment of neoplastic diseases, may also be considered for the treatment of PKD.

Alterations in intracellular calcium homeostasis and cyclic adenosine 3,5-phosphate likely underlie the increased cell proliferation and fluid secretion in polycystic kidney disease. Hormone receptors that affect cyclic adenosine 3,5-phosphate and are preferentially expressed in affected tissues are logical treatment targets. There is a sound rationale for considering the arginine vasopressin V_2 receptor as a target. The arginine vasopressin V_2 receptor antagonists OPC-31260 and tolvaptan inhibit the development of polycystic kidney disease in cpk mice and in three animal orthologs to human autosomal recessive polycystic kidney disease (PCK rat), autosomal dominant polycystic kidney disease (Pkd2/WS25 mice), and nephronophthisis (pcy mouse). PCK rats that are homozygous for an arginine vasopressin mutation and lack circulating vasopressin are markedly protected. Administration of V2 receptor agonist 1-deamino-8-D-arginine vasopressin to these animals completely recovers the cystic phenotype. Administration of 1-deamino-8-D-arginine vasopressin to PCK rats with normal arginine vasopressin aggravates the disease. Suppression of arginine vasopressin release by high water intake is protective. V2receptor antagonists may have additional beneficial effects on hypertension and

chronic kidney disease progression. A number of clinical studies in polycystic kidney disease have been performed or a recurrently active. The results of phase2 and 2-3studies indicate that tolvaptan seems to be safe and well tolerated in autosomal dominant polycystic kidney disease. A phase 3, placebo-controlled, double-blind study in 18- to 50-yr-old patients with autosomal dominant polycystic kidney disease and preserved renal function but relatively rapid progression, as indicated by a total kidney volume >750 ml, has been initiated.

Mammalian target of rapamycin (mTOR) is the core component of two complexes, mTORC1 and mTORC2. mTORC1 is inhibited by rapamycin and analogues. mTORC2 is impeded only in some cell types by prolonged exposure to these compounds. mTOR activation is linked to tubular cell proliferation in animal models and human autosomal dominant polycystic kidney disease (ADPKD).

mTOR inhibitors impede cell proliferation and cyst growth in polycystic kidney disease (PKD) models. After renal transplantation, two small retrospective studies suggested that mTOR was more effective than calcineurin inhibitor-based immunosuppression in limiting kidney and/or liver enlargement. By inhibiting vascular remodeling, angiogenesis, and fibrogenesis, mTOR inhibitors may attenuate nephroangiosclerosis, cyst growth, and interstitial fibrosis. Thus, they may benefit ADPKD at multiple levels. However, mTOR inhibition is not without risks and side

effects, mostly dose-dependent. Under certain conditions, mTOR inhibition interferes with adaptive increases in renal proliferation necessary for recovery from injury. They restrict Akt activation, nitric oxide synthesis, and endothelial cell survival (down-stream from mTORC2) and potentially increase the risk for glomerular and peritubular capillary loss, vasospasm, and hypertension. They impair podocyte integrity pathways and may predispose to glomerular injury.

Administration of mTOR inhibitors is discontinued because of side effects in up to 40% of transplant recipients. Currently, treatment with mTOR inhibitors should not be recommended to treat ADPKD. Results of ongoing studies must be awaited and patients informed accordingly. If effective, lower dosages than those used to prevent rejection would minimize side effects. Combination therapy with other effective drugs could improve tolerability and results.

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disease characterized by a prolonged subclinical course of gradual renal cyst expansion, resulting in massively enlarged kidneys and renal failure by the fifth to sixth decade. Renal cyst expansion results in intrarenal ischemia and activation of the renin-angiotensin-aldosterone system (RAAS) and relates to the development and maintenance of hypertension in ADPKD. Hypertension relates to disease progression in

Summary

ADPKD with regard to renal volume, proteinuria, cardiovascular complications, and progression to end-stage renal disease. Novel magnetic resonance imaging methods developed in the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) provide accurate estimates of change in renal volume over a short period of time in ADPKD patients with intact renal function. In CRISP an increase in renal volume of 63.4 ml/yr was found. PKD1 status, male gender, hypertension, reduced renal blood flow, and proteinuria are associated with increased renal volume and change in renal volume over time. HALT-Polycystic Kidney Disease (HALT-PKD) is designed to test whether blockade of RAAS and/or rigorous blood pressure control play a role in slowing renal progression during early (using magnetic resonance imaging methods developed in CRISP) and during late (using measures, including composite of time to doubling of serum creatinine, onset of end-stage renal disease, or death) phases in ADPKD. Findings from CRISP and the rationale for interventions in ADPKD are described, and the design of the HALT-PKD clinical trial is outlined.