Recent advances in the clinical management of autosomal-dominant polycystic kidney disease

Autosomal-dominant polycystic kidney disease (ADPKD) is an inherited disorder usually manifest in adulthood. It is characterized by the development of multiple renal cysts variably associated with extrarenal (mainly hepatic and cardiovascular) abnormalities. With a prevalence rate ranging from 1:400 to 1:1000 in White populations, ADPKD is one of the most common genetic diseases and by far the most frequent inherited nephropathy. ADPKD currently accounts for 3–10% of all patients admitted for maintenance dialysis in Western countries.

Over the past decade, major progresses have been achieved in the understanding of the molecular basis of the disease. The gene incriminated in about 85% of cases, PKD1, has been located on chromosome 16 in 1985 and identified in 1994. A second gene, PKD2, accounting for the vast majority of the other cases, has been mapped on chromosome 4 in 1993 and was cloned this year. The existence of a third gene is suggested by recent reports. Using various strategies, a number of researchers have competed to unravel the complete sequence of the PKD1 gene and predict the structure of the corresponding protein, called polycystin. Polycystin appears to be an integral membrane glycoprotein probably involved in cell–cell and/or cell–matrix interaction. Preliminary evidence suggests that the PKD2 protein functions as an ion channel or pore. Polycystin could act as the regulator of the PKD2 channel activity. How mutations in PKD1 and PKD2 lead to cyst development and other clinical abnormalities remains to be understood. Elucidation of this mechanism should pave the way to pharmacological intervention with the hope to prevent or, more realistically, arrest or slow the manifestations of the disease. Meanwhile, patients with ADPKD already benefit from various recent progresses in the clinical management of the condition. This editorial attempts to provide a concise update of the advances in the management of renal, hepatic and cerebral complications of ADPKD.

For the few patients suffering from chronic renal pain resistant to common analgesics, Elzinga et al. (1992) re-examined the role of cyst decompression, a technique abandoned in the 1960s because of its reportedly detrimental effect on renal function. They reported on surgical decompression (100–200 cysts unroofed per kidney) in 30 patients, with sustained pain relief (up to 4 years later) in 62%. Laparoscopic cyst decortication now appears as a promising, minimally invasive alternative.

Renal cyst infection may pose a therapeutic problem. It has long been known that the response to standard antibiotic regimens is often inadequate despite in vitro sensitivity of the infecting organism. As clearly shown by Bennett and Elzinga (1993) this results from poor penetration of conventional antibiotics across the cyst wall due to their lipophilia. The advent of lipophilic antibiotics active against gram-negative bacteria—trimethoprim-sulfamethoxazole and fluoroquinolones—has greatly facilitated the treatment of this complication.

Renal calculi are diagnosed in about 20% of patients with ADPKD. As they are frequently constituted of uric acid, they may be radiolucent. Contrary to initial fears, obstructive or symptomatic stones can be safely treated by the techniques commonly used in the general population, including percutaneous and extracorporeal lithotripsy.

Hypertension is an early and very common manifestation of ADPKD. An elevation of blood pressure, still within the normal range, is detectable in young affected people and probably accounts for their increased left ventricular mass. Intrarenal activation of the renin-angiotensin system appears to play a central pathogenic role, as witnessed by haemodynamic and morphologic studies. Consequently, ACE inhibitors are logical first-line agents for the treatment of hypertension in ADPKD. Early control of blood pressure is mandatory, as cardiovascular complications are a leading cause of death in ADPKD.

Progressive renal failure is the most serious complication of ADPKD. Once glomerular filtration rate is lower than 50 ml/min, rate of decline averages 5 ml/min/year, which is faster than in other primary renal diseases. Recent epidemiological data have
Symptomatic patients may now benefit from various procedures aimed at reducing the volume of the cysts. When symptoms are caused by a small number of large, accessible cysts, percutaneous drainage and sclerosis with alcohol or minocycline or laparoscopic fenestration should be considered; in patients with severe symptoms and multiple cysts, partial hepatic resection combined or not with fenestration is the preferred option; in the very rare patient with extensive liver disease with no spared hepatic segment of the liver, liver transplantation may be considered.37,38

Besides cysts, other liver changes, previously thought to be restricted to autosomal-recessive polycystic kidney disease, namely congenital hepatic fibrosis and idiopathic dilatation of the intra- or extrahepatic biliary tract, have occasionally been reported in ADPKD.1 Treatment of portal hypertension and cholangitis does not differ from that in the general population.

Although the association of intracranial aneurysm (ICA) and ADPKD has been established for many years, it is only recently that an accurate assessment of its prevalence has been possible by high-resolution computerized tomography (CT) and magnetic resonance angiography. Combining three large prospective series, the prevalence of asymptomatic ICA in ADPKD is about 8% overall, and reaches 16% in the subgroup with a family history of ICA or subarachnoid haemorrhage.39

The risk of suffering a rupture of an ADPKD-associated ICA is as yet ill-defined. ICA rupture results in subarachnoid haemorrhage, the cardinal feature of which is sudden, incredibly severe headache. Neurologists have taught us that in 20 to 40% of cases, the event has been preceded, by from a few hours up to two weeks, by premonitory headaches (due to a first leak from the ICA): doctors should thus be alerted by headaches of sudden onset or unusual character or severity. The current first-line procedure for diagnosing subarachnoid haemorrhage is non-enhanced CT scanning. In the near future, initial work-up will most likely include contrast-enhanced spiral CT, providing additional information about the site of the ruptured ICA. The management of ICA rupture has been reviewed elsewhere.40 The standard treatment remains surgical clipping, but endovascular occlusion has emerged as a valuable, increasingly used, alternative.

Given the grave prognosis of ICA rupture and the recently established possibility of detecting and repairing it before rupture, screening for ICA has been considered. The benefits of screening have to be balanced with the risk of prophylactic surgery. Since the original Levey’s decision analysis,40 this issue has been re-examined by several authors, taking into account new information on prevalence of ICA, accuracy of screening tests, outcome of prophylactic
treatment and probability of rupture. On the basis of updated decision analyses, we now recommend screening ADPKD patients aged 18–40 who have a family history of ICA. Screening is performed either by magnetic resonance angiography or spiral CT. How frequently at-risk patients with a negative screening test should be re-evaluated remains to be determined.

In conclusion, although the main hope is that the latest genetic breakthroughs are the starting point of a major therapeutic advance, we should not overlook the progresses made lately in the clinical management of ADPKD-related complications. A balanced use of the powerful tools and techniques made recently available should further improve the quality of life of our patients.

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References


