Diagnosis and Management of Autosomal Dominant Adult Polycystic Kidney Disease

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AUTOSOMAL DOMINANT POLYCYSTIC kidney disease (ADPKD) is the most common genetic disease of the kidney, affecting approximately one in every 1,000 individuals of all races. It is the cause of end-stage renal disease (ESRD) in 5 to 10 percent of American and European ESRD populations. The disease is characterized by the development of renal and extra-renal cysts in an age-dependent manner. The kidneys can be massively enlarged and the size of the cystic kidneys correlates with complications such as painful cyst rupture, hematuria, hypertension and progressive renal failure. ADPKD is associated with a number of extra-renal co-morbidities including valvular cardiac defects, inguinal hernias, diverticulosis and intracranial arterial aneurysms.

ADPKD is genetically heterogeneous. Mutations of two genes, PKD1 and PKD2, account for 85 and 15 percent of cases, respectively. The major distinction between the two is that PKD1 mutations generally result in earlier onset of ESRD — an average of 54 years versus 74 years (Hateboer N., et al. *Lancet* 1999; 353:103). The diagnosis of overt ADPKD is straightforward when an affected patient presents with enlarged kidneys, multiple bilateral cysts and a family history consistent with autosomal dominant inheritance (i.e., 50 percent of children and siblings affected). However, a family history may be absent in 20 percent of newly diagnosed patients. Renal ultrasonography is the imaging modality of choice for screening of at-risk individuals. Using DNA linkage analyses as the gold standard, age dependent ultrasonographic diagnostic criteria have been developed. For at-risk individuals between 15 and 29 years of age, the presence of at least two renal cysts (unilateral or bilateral) is diagnostic. For those between 30 and 59 years of age, at least two cysts in each kidney are required for diagnosis, and for those over the age of 60, at least four cysts in each kidney are required (Pei Y., *Clin J Am Soc Nephrol* 2006; 1:1108).

Molecular genetic testing is now available for ADPKD and may be useful for evaluation of at-risk individuals with atypical imaging results, or for younger at-risk individuals being evaluated as living kidney donors. DNA linkage analysis requires both the genotype and clinical information from multiple affected and unaffected members as well as from the at-risk individual. Bayesian algorithms then provide a probability estimate of linkage of the family to a disease locus. Prediction of disease in an at-risk individual is highly accurate with an error of less than 1 percent when multiple family members provide blood and clinical information, but the findings are less conclusive in small families. The other molecular approach to diagnosis relies on gene-based mutation screening. The main advantage is that the test requires a blood sample only from the test subject. However, definitive mutations are found in only two-thirds of subjects with AKPD, so this expensive screening test is only useful when it is positive. For evaluation of potential live kidney donors, DNA linkage analyses are preferred when at least three affected family members are available. For smaller families, gene mutation screening of a potential donor is recommended only if a discrete mutation can first be identified in the potential recipient (Huang E., et al. *Transplantation* 2009; 87: 133).

In early clinical trials, the vasopressin antagonist, Tolvaptan, has shown some promise in reducing cyst size and delaying the progression of ADPKD to ESRD (Torres V.E., et al. *N Engl J Med* 2012; 367: 2407). However, the drug is not yet FDA-approved for this indication. Kidney transplantation is the renal replacement therapy of choice for patients with ADPKD, although unilateral or bilateral nephrectomies may be required prior to transplantation in patients with massively enlarged kidneys. Compared to patients with other underlying kidney diseases, those with ADPKD exhibit superior allograft survival rates, possibly related to the fact that they are more often transplanted preemptively.

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