THE DIAGNOSIS AND PROGNOSIS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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Abstract. Background. Autosomal dominant polycystic kidney disease is usually caused by a mutant gene at the PKD1 locus on the short arm of chromosome 16, but in about 4 percent of families with the disorder it is caused by unknown mutations elsewhere in the genome. The natural course of the disease in both genetic forms is not well characterized.

Methods. We studied 17 families with autosomal dominant polycystic kidney disease to compare presymptomatic diagnosis by ultrasonography with diagnosis by genetic-linkage studies and to relate clinical variation of the disease to whether the PKD1 mutation was implicated.

Results. In 10 families the disorder was found to cosegregate with polymorphic DNA markers flank ing the PKD1 locus, in 2 families it did not, and in 5 families linkage could not be determined. In the 10 families with the PKD1 mutation, 46 percent of the members less than 30 years old who had a 50 percent risk of inheriting a mutation had renal cysts, as compared with 11 percent of the members of the two families without linkage (P<0.001). In the PKD1 families, all 67 diagnoses made by ultrasonography were confirmed by determination of the genotype as inferred from linkage. Forty of 48 members (83 percent) less than 30 years old who inherited the PKD1 mutation had renal cysts. All 27 members 30 years old or older who inherited the mutation had renal cysts, suggesting that the probability of a false negative diagnosis did not exceed 0.13 in this age group (P<0.05).

The mean (±SE) age at the onset of end-stage renal disease among members of the PKD1 families was 56.7±1.9 years, as compared with 69.4±1.7 years among members with cysts in the families without linkage (P = 0.0025). Hypertension and renal impairment were less frequent and occurred later in the families without the PKD1 mutation.

Conclusions. At present, in most persons with a 50 percent risk of autosomal dominant polycystic kidney disease, imaging techniques are the only mode of reaching a diagnosis before symptoms appear. In such persons a negative ultrasonographic study during early adult life indicates that the likelihood of inheriting a PKD1 mutation is small. In the few who inherit a non-PKD1 mutation for polycystic kidney disease, renal failure is likely to occur relatively late in life. (N Engl J Med 1990; 323:1085-90.)

AUTOSOMAL dominant polycystic kidney disease is responsible for 6 to 9 percent of cases of end-stage renal disease in North America1,2 and Europe.3 About 1 in 1000 persons carries a mutant gene for this condition.4 The disease can be diagnosed before symptoms develop by ultrasonographic imaging of the kidneys for renal cysts. Because these cysts are ordinarily not detectable in children but become more numerous and larger with age, the interpretation of negative findings is age-dependent.5

One locus for autosomal dominant polycystic kidney disease, designated PKD1, has been localized to the short arm of chromosome 16.6-8 In most families studied, the disease is co-inherited with genetic markers near PKD1,9 but in about 4 percent of families the disorder is due to mutations elsewhere in the genome.10-12 Thus, although linkage studies allow accurate presymptomatic diagnosis of the disease when it is due to PDK1, this approach cannot be used when the disease is due to other causes. Moreover, as in the study of other inherited disorders,13 sufficient family information for linkage studies may not be available.

The age at onset of renal dysfunction due to autosomal dominant polycystic kidney disease varies widely. Although renal failure develops in many persons with the condition when they are in middle age, a considerable proportion remain asymptomatic,4,14,15 so that the frequency of polycystic kidneys found at autopsy in persons dying without clinical renal disease is greater than the clinical prevalence of autosomal dominant polycystic kidney disease would suggest.16 The prob-
ability that end-stage renal disease will develop by the age of 58 years has been estimated to be 0.53, but the uncertainty of this estimate is large (95 percent confidence interval, 0.34 to 0.72) because few patients more than 50 years old have been studied.15 Whether the progression of disease caused by mutations at the PKD1 locus differs from that of disease caused by mutations elsewhere is unknown. Hypertension, nephrolithiasis, or urinary tract infections may occur early in the disease,17–20 and in many patients serum creatinine levels may remain elevated for several years before end-stage renal disease develops.16

Persons who may have inherited a condition with variable but potentially serious clinical manifestations need precise information about their prognosis. We therefore studied 17 families with autosomal dominant polycystic kidney disease,5,14 with the following goals: to assess the sensitivity and specificity of ultrasonographic and genetic-linkage studies for presymptomatic diagnosis; to determine the distribution of cases of end-stage renal disease related to PKD1 mutations and non-PKD1 mutations, according to the age at onset; and to evaluate the prevalence of hypertension, nephrolithiasis, urinary tract infections, and elevated serum creatinine levels in affected members of families with and without PKD1 mutations.

**METHODS**

**Identification of Families and Affected Members**

We contacted nephrologists and urologists in Newfoundland and Labrador to identify all persons in the province who were receiving treatment for autosomal dominant polycystic kidney disease.14 The diagnosis was considered confirmed when documented in any of the following ways: by an autopsy report; by report of a death due to chronic renal failure, with a clinical diagnosis of autosomal dominant polycystic kidney disease; by a surgical report; by excretory urography or computed tomography; or by unequivocal findings on ultrasonography (see below). We then attempted to contact and evaluate all family members residing in Newfoundland and Labrador who were at risk because they had an affected parent, sibling, or child. The first member identified in each family was designated the index case and was excluded from analysis.

**Ultrasonographic Diagnosis**

In our initial studies,5,14 all participating family members underwent ultrasonographic scanning of each kidney in the sagittal and transverse planes. (Scanning was performed with either the Model 2130 ADR Ultrasound Real-Time Scanner [ADR Ultrasound, Tempe, Ariz.] or the Picker Echo Dynamic Control Scanner and Picker 80 Linagraph Digital Imager [Picker, Cleveland].) All scans were performed under the supervision of one ultrasonographer and interpreted in blinded fashion by one radiologist. Subsequently, all participating family members who were not found to have cysts on initial study or who had not previously been evaluated underwent scanning in real time (performed with either an Ultramark 8 [Advanced Technology Laboratories, Washington, D.C.] or a Sonoline SL2 [Siemens, Pleasanton, Calif.]). The majority of these scans were performed by one radiologist, who also interpreted all scans.

Autosomal dominant polycystic kidney disease was diagnosed when at least one cyst was present in each kidney and when one kidney had more than one cyst.2 When these criteria were not met ultrasonography suggested cystic disease, the findings were considered equivocal. In population studies, less than 2 percent of children21 and 10 percent of young adults22 have simple renal cysts, and simple cysts of both kidneys are even less frequent. Therefore, these diagnostic criteria are conservative when applied to persons with a 50 percent risk.

**Clinical Manifestations**

The age at the onset of end-stage renal disease was taken to be the age at which long-term replacement therapy for renal function became necessary or, in persons who died of renal failure before such treatment became available, the age at death.

Blood-pressure measurements were made with the subjects seated, after three minutes’ rest; the fifth Korotkoff sound was used to determine the diastolic pressure. Subjects were classified as hypertensive if the systolic or diastolic blood pressure exceeded the 95th percentile for their age and sex23–25 or if they were taking antihypertensive agents.

Serum creatinine was measured with an AutoAnalyzer. Creatinine clearance was calculated according to the formula of Cockcroft and Gault.26 Renal impairment was indicated by a creatinine clearance of less than 1.2 ml per second (70 ml per minute), a serum creatinine level above 120 μmol per liter when creatinine-clearance values were not available (16 subjects), or the presence of end-stage renal disease.

Any history of renal calculi and treatment of urinary tract infections was obtained by the research nurse during the interview of each family member.

**Linkage Studies**

Each family was evaluated for the coinheritance of autosomal dominant polycystic kidney disease and alleles at polymorphic DNA sites (marker loci) flanking the PKD1 locus in order to distinguish families with disease due to mutations at this locus from families with disease due to mutations elsewhere and, within families with the PKD1 mutation, to identify members with a mutation. The probes used to detect polymorphism flanking the PKD1 locus were VK58, 24.1, and 909a, which identify polymorphism between PKD1 and the centromere of chromosome 16, and 3’HVR, CMM65a, and PNL56, which identify polymorphism distal to PKD1.27,28 The coinheritance of marker alleles with disease phenotypes was assessed by inspection of each pedigree. When alleles on both sides of PKD1 cosegregated with the disease, the inheritance of a PKD1 mutation could be inferred with a high degree of confidence, since the likelihood of error is approximately equal to the likelihood of double recombination, which, for marker loci separated by recombination fractions of less than 10 percent, is low.8

Prior probabilities that autosomal dominant polycystic kidney disease is due to a PKD1 mutation exceeds 0.95.12 Therefore, if a family had two members with coinheritance of the disease phenotypes (i.e., affected or unaffected) and marker alleles, in addition to those used to predict which alleles were segregating with the mutant and normal PKD1 alleles, autosomal dominant polycystic kidney disease was considered to be due to a PKD1 mutation in that family. If the presence of cystic kidneys did not cosegregate with alleles at marker loci flanking PKD1 in two or more family members, the family was considered to have polycystic kidney disease due to a mutation elsewhere in the genome.

**Statistical Analysis**

The sensitivity and specificity of ultrasonographic diagnosis of the PKD1 form of polycystic kidney disease were assessed by comparing ultrasonographic diagnoses with diagnoses based on the coinheritance of flanking marker alleles in families with the PKD1 mutation.

The Kaplan–Meier29 method was used to calculate survival to the onset of end-stage renal disease or death in all persons with autosomal dominant polycystic kidney disease, and to compare the survival of persons with cysts in families with the PKD1 mutation and in families without this mutation.

Two-tailed chi-square tests were used to compare the rates of hypertension, renal impairment, renal stones, and treated urinary
tract infections in persons with and persons without renal cysts in all families, families with the PKD1 mutation, and families without the mutation, and to compare persons with cysts in both groups of families. Persons without cysts were considered to be family members not at risk of autosomal dominant polycystic kidney disease as determined by linkage studies, persons 30 years old or older who were not found to have cysts on ultrasonographic examination and their children, and spouses of family members. Persons with endstage renal disease were excluded from the analysis of rates of hypertension.

**RESULTS**

**Proportion of Families with PKD1 Mutations**

In 10 families, chromosome 16 marker alleles and polycystic kidney disease phenotypes were inherited together. In two large families, phenotypes and chromosome 16 marker alleles were inherited independently, which ruled out a PKD1 mutation as the cause of the disease. In five families, cosegregation of markers and disease could not be confirmed or excluded. In four of these five families, too few members were available for evaluation; in the fifth — a group of siblings comprising nine members in the third and fourth decades — four members had polycystic kidney disease, four did not, and one had equivocal findings on ultrasonography. The ultrasonographic phenotypes in this group were not consistently associated with chromosome 16 marker alleles, possibly because cysts had not yet developed in some members. The parents of the group of siblings had died, and no member had affected children, making it impossible to extend the linkage study.

**Ultrasonographic Diagnosis**

Ultrasonographic examinations of 290 persons with a 50 percent risk of autosomal dominant polycystic kidney disease showed that the proportion with renal cysts was age-dependent and lower in the families without the PKD1 mutation than in families with this mutation. Among 125 members of PKD1 families at risk who were less than 30 years old, 58 (46.4 percent; 95 percent confidence interval, 37.6 to 55.1 percent) had autosomal dominant polycystic kidney disease, as compared with 3 of 27 members of the two families without linkage (11.1 percent; 95 percent confidence interval, 2.4 to 29.2 percent; P<0.001). Among persons with a 50 percent risk who were 30 years old or older, 36 of 70 members (51.4 percent; 95 percent confidence interval, 30.2 to 63.9 percent) of the families with the PKD1 mutation had autosomal dominant polycystic kidney disease, as compared with 13 of 28 members (46.4 percent; 95 percent confidence interval, 27.5 to 66.1 percent) of the two families without linkage.

**Correspondence between Ultrasonographic Diagnosis and Genotype in PKD1 Families**

In 126 persons with a 50 percent risk of inheriting a PKD1 mutation, ultrasonographic diagnoses were compared with genotypes inferred from linkage studies (Table 1). In none of these persons was a positive ultrasonographic diagnosis at variance with the genotype. Discordance between negative ultrasonographic findings and genotypes was age-dependent. Of 48 persons less than 30 years old who inherited a PKD1 mutation, 7 did not have renal cysts and 1 had an equivocal ultrasonographic result; of 27 persons 30 years old or older, all had cysts on ultrasonographic examination. This observation is consistent with the calculation that the probability of a false negative ultrasonographic diagnosis in persons 30 years old or older will not exceed 0.13 (the upper limit of the 95 percent confidence interval for 0 of 27).

**End-Stage Renal Disease**

Figure 1 shows the cumulative survival to the time of onset of end-stage renal disease in all persons with ultrasonographic or clinical evidence of disease (PKD1 or non-PKD1 form) or with a PKD1 mutation in 17 families. The earliest age at onset was 30 years. Twenty-five percent of these persons had endstage renal disease by the age of 47 years, 50 percent by the age of 59, and 75 percent by the age of 70. The mean (±SE) age at onset of end-stage renal disease (or at death) was 59.3±1.8 years, as compared with a mean age at death of 74.1±1.8 years among unaffected family members.

The mean survival to the onset of end-stage renal disease (or to death) was shorter among persons with disease due to a PKD1 mutation than among persons with a non-PKD1 form of disease (56.7±1.9 vs. 69.4±1.7 years; P = 0.025) (Fig. 2).

**Hypertension**

Hypertension was significantly more prevalent among persons with renal cysts than among those without cysts (Table 2). A comparison of persons with cysts in the 10 families with PKD1 disease with those in the 2 families without linkage suggested that hypertension occurred less often and later in life in the latter.

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<th>Table 1. Presence of Renal Cysts Detected by Ultrasonography and Inferred from Genotypes in Persons in PKD1 Families Who Had a 50 Percent Risk of Autosomal Dominant Polycystic Kidney Disease.</th>
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*ADPKD denotes the genotype for autosomal dominant polycystic kidney disease.
group, although the differences between the groups were not statistically significant.

**Other Renal Disease**

The majority of persons with renal cysts who were 40 years old or older had some degree of renal impairment, as did some younger than 40 years; like the other manifestations of autosomal dominant polycystic kidney disease, renal impairment was less frequent in the two families without linkage (Table 3). Persons with autosomal dominant polycystic kidney disease did not report a history of renal stones significantly more often than did unaffected family members (15 percent [16 of 108] vs. 10 percent [20 of 209]). Similarly, persons with autosomal dominant polycystic kidney disease did not report a history of urinary tract infections more frequently than did unaffected family members (22 percent [24 of 109] vs. 17 percent [35 of 206]).

**DISCUSSION**

**Genetic Heterogeneity and Presymptomatic Diagnosis**

The diagnosis of autosomal dominant polycystic kidney disease before the onset of symptoms is most conveniently made by ultrasonography. The demonstration of renal cysts unambiguously establishes the diagnosis at any age, and by early adulthood, negative ultrasonographic results provide considerable assurance that a person is not affected.

About 4 percent of patients with autosomal dominant polycystic kidney disease do not have PKD1 mutations. For this reason, extensive information about a patient’s pedigree is always required in order to demonstrate confidently that the disease is cosegregating with chromosome 16 markers and that these markers can be used in diagnosis. In populations less geographically stable than that of Newfoundland, most families do not have enough members available for linkage analysis, let alone the detection of genetic heterogeneity. A study of a series of 148 families identified in Denver is illustrative; 75 families were represented by only one person, and only 29 families (20 percent) by four or more persons.

Nonetheless, genetic-linkage testing can identify affected persons whom ultrasonography cannot, if a PKD1 mutation is present. It has been recommended that linkage testing be made available to adults with a 50 percent risk of autosomal dominant polycystic kidney disease who request testing, to potential transplant donors related to potential recipients, to adults with a 50 percent risk whose medical therapy might be predicated on knowledge of their gene status, and to children with a 50 percent risk who are in unusual clinical circumstances. Prenatal testing is also possible. Genetic-marker studies seem most justified when a diagnosis is desired in an asymptomatic person less than 30 years old whose family provides enough information for genetic heterogeneity to be detected and in whom ultrasonography is negative. The problems of linkage diagnosis of the PKD1 mutation will finally be overcome when the PKD1 gene is cloned and direct detection of mutations becomes possible.

The key members of a family who identify it as one in which polycystic kidney disease is not due to a PKD1 mutation are those with polycystic kidneys who would have to be double recombinants if the disease were in fact due to a PKD1 mutation. Because the prior probability that autosomal dominant polycystic kidney disease is due to a PKD1 mutation is approximately 0.96, whereas the prior probability of nonlinkage is only 0.04, the conclusion that disease in a family is not due to a PKD1 mutation is highly dependent on the assumption that members whose marker genotypes are not compatible with PKD1 linkage are in fact affected. We observed no false positive diagnoses while comparing ultrasonographic findings with tests for PKD1 marker genotypes.

Imaging serves as the only method of diagnosis in persons at risk whose family data are insufficient for
linkage analysis and in members of the few families known to have disease not due to PKD1. In persons in whom the results of ultrasonographic imaging are negative or equivocal, a repeat examination after the age of 30 years may clarify the diagnosis or computed tomographic imaging may verify the presence of renal cysts.

Clinical Course of Autosomal Dominant Polycystic Kidney Disease

The most important manifestation of autosomal dominant polycystic kidney disease is renal failure. We therefore obtained age-specific estimates of the probability of end-stage renal disease or a fatal complication of polycystic kidney disease in asymptomatic persons with renal cysts. When all such persons were considered as a group, the mean survival to end-stage renal disease or death was 59.3 years; survival in those with PKD1 mutations was 56.7 years, and survival in those with the non-PKD1 form of disease was 69.4 years. These results indicate a prognosis that is less grim than that determined in earlier studies, which included only patients with symptoms, and are consistent with surgical and postmortem data showing that at least 50 percent of persons with polycystic kidneys have no recorded symptoms and that asymptomatic persons have approximately normal life spans.

Early diagnosis and control of hypertension and restriction of dietary protein intake may slow the progression of renal impairment. Such possibilities justify the diagnosis of autosomal dominant polycystic kidney disease before symptoms occur. Hypertension occurred in 25 percent of the children and young adults with renal cysts in the families of this study and in 62 percent of adults with cysts (but without end-stage renal disease) — rates similar to those in other studies. Our finding of renal impairment in 9 percent of persons with kidney cysts who were 20 to 39 years old and in more than 60 percent of those who were 40 years old or older is comparable with observations reported by Zeier et al., found that the median age at the time of first elevation of the serum creatinine level was 38 years in men and 39 years in women.

Unlike other investigators, we did not find a history of nephrolithiasis to be significantly more common among persons with autosomal dominant polycystic kidney disease than among their unaffected relatives. This finding may reflect the relatively high prevalence of nephrolithiasis in Newfoundland. Treated urinary tract infections were not reported significantly more frequently by persons with autosomal dominant polycystic kidney disease.

Clinical Variation and Genetic Heterogeneity

In the 2 large families with non-PKD1 disease described here, the average age at the onset of end-stage renal disease was later than in the 10 families with PKD1 mutations, as was the appearance of ultrasonographically detectable renal cysts. Hypertension and renal impairment also tended to occur later. Similarly, in a large family studied in Denver, in which autosomal dominant polycystic kidney disease did not cosegregate with chromosome 16 markers, the mean age at diagnosis was relatively late. It remains to be determined whether disease not due to the PKD1 mutation is a single genetic entity, and it is premature to conclude that it is ordinarily less severe than PKD1 disease.

The PKD1 form of autosomal dominant polycystic kidney disease is not invariably more severe than the non-PKD1 form. A four-generation family has been described in which the disorder cosegregated with chromosome 16 markers but no member had symptoms. On the other hand, PKD1 disease occasionally occurs in infancy and childhood, although it did not in the Newfoundland families we studied.

Our findings indicate that persons with a 50 percent risk who are older than 30 years and who do not have ultrasonographically detectable renal cysts may be told that they are unlikely to have autosomal dominant polycystic kidney disease, because it is unlikely that they have inherited a PKD1 mutation. There is a
small probability that autosomal dominant polycystic kidney disease in their family is due to a mutation at another locus; if so, and if renal cysts develop, renal failure is not likely to occur until relatively late in life.

The persons participating in this study were interested in learning their ultrasonographic results and genotypes, but it is understandable that some persons at risk may be ambivalent toward the diagnosis of autosomal dominant polycystic kidney disease before the development of symptoms. This perception may change if it can be demonstrated that interventions such as the control of hypertension or restriction of dietary protein retard or prevent the progression of renal failure, or if characterizing the mutant gene products responsible for autosomal dominant polycystic kidney disease permits more specific therapies to be developed.

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References