Autosomal Dominant Polycystic Kidney Disease in Blacks: Clinical Course and Effects of Sickle-Cell Hemoglobin[1]

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a frequent cause of ESRD, but its frequency in blacks has not been well delineated and its course and the effects of sickle hemoglobin in this disease in blacks have not been previously reported. The occurrence of ADPKD in blacks and whites was determined in two ESRD populations: all ESRD patients seen over a 16-yr period in one area of Southeast Tennessee and all ESRD patients in 15 hemodialysis units in Tennessee and Atlanta, GA. The frequency of sickle hemoglobin was determined and compared in a group of nonrelated blacks with ESRD with and without ADPKD. The age at onset of ESRD and factors that might affect ADPKD such as gender, hypertension, and hemoglobin type were examined. ADPKD was a less frequent cause of ESRD in blacks than whites (1.4 versus 6.8%). However, after adjusting for the population rate, the incidence rates in blacks and whites were similar (0.48 and 0.47 of 100,000). There was a higher incidence of sickle hemoglobin in nonrelated blacks with ADPKD versus other black ESRD patients (50 versus 7.5%; $P < 0.005$). Blacks had an earlier onset of ESRD than whites (43.2 versus 55.4 yr; $P < 0.0001$), as did blacks with sickle-cell trait versus blacks without (38.2 versus 48.1 yr; $P < 0.003$). In this population, hypertension and gender had no effect on the onset of ESRD. ADPKD accounted for a smaller percentage of blacks than whites with ESRD because of the high percentage of blacks with renal disease from other causes. However, the frequency of ESRD due to ADPKD was similar in blacks and whites. Sickle-cell hemoglobin occurred more frequently than expected, and there was evidence of more severe disease as measured by earlier onset of ESRD in blacks when compared with whites and blacks with sickle-cell trait when compared with blacks without the trait.

Key Words: *Autosomal dominant polycystic kidney disease, ESRD, β^S gene cluster haplotype, sickle-cell anemia, hypertension*

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease in the United States, affecting an estimated 1 in 500 to 1 in 1,000 people. However, in this country, the frequency may not be uniform among all racial groups. Several studies of ESRD patients have reported that blacks may be affected less often than whites (1,2). In this regard, ADPKD has been reported to be uncommon in Africa (3). However, the United States Renal Data System reports an ESRD prevalence ratio based on population per million that is similar in blacks and whites (4,5). Even if this inherited kidney disease was less prevalent in blacks, the incidence of ESRD might be similar if renal failure occurs more frequently in blacks than in whites with ADPKD. It is not known if the course of ADPKD is similar in blacks and whites. However, in blacks, ESRD is two to six times more frequent for most renal disease (hypertension, diabetes mellitus, glomerulonephritis) and occurs on average 5 yr earlier (57 versus 62 yr of age) (4,5). Therefore, to address these issues of incidence and the course of ADPKD in blacks, we studied two populations of patients. Comparisons were made between white and black ADPKD patients with regard to occurrence, age of onset of ESRD, and the effects of gender and hypertension on the course of the disease. In addition, the possible association between ADPKD and sickle-cell

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trait (AS) has been considered by two of us (6). A formal examination of this association is undertaken in this study.

METHODS

Two study populations were used. The first study group was a patient population enrolled in the ESRD program in Chattanooga, TN, from 1975 to 1990. All of the patients had been cared for by one of the authors (J. Yium) or one of his associates. The renal group was the only one in the county area and cared for all the ESRD patients undergoing dialysis or transplantation. The diagnosis of ADPKD was based on family history and a characteristic iv pyleogram, nephrotomogram, or ultrasonogram displaying numerous bilateral renal cysts. All patients had renal imaging studies.

The second study group used was composed of the hemodialysis and peritoneal dialysis patients currently undergoing treatment in 15 dialysis units operated by Dialysis Clinic, Incorporated (DCI), in Tennessee and Atlanta, GA, in 1990. These clinics had a high percentage of black patients. In this group of patients, the diagnosis of ADPKD was ascertained by a questionnaire. The medical charts of patients who indicated a diagnosis of ADPKD were reviewed and confirmed by criteria similar to those used in the Chattanooga cohort. It is uncertain if renal imaging studies had been done on all of the black ESRD patients in this survey, so some diagnoses of polycystic kidney disease may have been missed. All black patients with ADPKD in both groups were interviewed and their medical records were reviewed, as were all white ADPKD patients from the Chattanooga cohort. Race was self-assigned.

A group of unrelated probands was used to determine the frequency of sickle-cell trait in blacks with ADPKD. There were 13 probands, 12 with ESRD: 3 each from the Chattanooga hemodialysis cohort and the DCI survey, and 4 patients previously encountered at the VA Hospital and Ben Taub Hospital in Houston, TX, by two of the authors (J. Yium and M. Martinez-Maldonado). Also, there were three referrals to the author (J. Yium) who were not part of the regular Chattanooga hemodialysis patient population. These included transient hemodialysis patients and patients seen for transplant evaluation. One of the probands was known to have had sickle-cell trait, but the hemoglobin status of all of the others was unknown at the time of the encounter. After informed consent was obtained, patients were tested for sickle-cell hemoglobin by hemoglobin electrophoresis. In four patients from earlier years of the study, the diagnosis of sickle-cell trait was based on a positive sickle-cell preparation without a history of anemia before ESRD. For comparison, 80 randomly selected unrelated black patients from the Chattanooga cohort with ESRD as a result of diseases other than ADPKD were tested for sickle-cell trait with hemoglobin electrophoresis after giving informed consent. No patients were excluded because of prior known sickle-cell trait, nor was any patient selected for study on the basis of sickle-cell trait.

For determining the time of ESRD onset and the effects of gender and hypertension, the cohort consisted of the 12 unrelated ESRD probands, 10 family members from four of the probands, and an additional proband from the DCI survey not tested for sickle-cell trait. The time of ESRD was considered to be the start of renal replacement therapy with hemodialysis, peritoneal dialysis, transplantation, or death from uremia. Hypertension was considered to be present if the blood pressure was more than 140 mm Hg systolic or more than 90 mm Hg diastolic or if the patient was being treated for hypertension with antihypertensive medications, excluding diuretics. The time of recording of the hypertension was at the onset of ESRD. Information on hypertension was not available for all subjects. All white ADPKD patients from the Chattanooga cohort were used for comparison.

The incidence ratio of ESRD due to ADPKD for blacks and whites was determined for Hamilton County, TN (the county seat for Chattanooga) on the basis of the census for the years 1970, 1980, and 1990 and the number of ESRD patients with ADPKD from this county between 1975 and 1990. χ^2 tests were used to assess the associations between two discrete factors; Fisher's exact test was used when the sample sizes were small. Two sample t tests, analysis of variance, and analysis of covariance were performed to compare the age of onset of ESRD between patient groups. P values are reported; statistical significance was considered to be present if P was less than 0.05.

RESULTS

Occurrence of ADPKD

Sixty-seven percent or 718 of the 1,076 patients enrolled in the Chattanooga ESRD program from 1975 to 1990 were white and 33% (358) were black (Table 1). In 6.8% of the white patients and 1.4% of the black patients, the ESRD was due to ADPKD ($P < 0.001$). In this population, the relative risk of ESRD due to ADPKD, as estimated by the odds ratio, was five times greater if the subject was white as compared with black. In the survey of Dialysis Clinic, Inc., centers in 1990, a greater percentage of the patients were black compared with the frequency observed in the Chattanooga study from 1975 to 1990 (62 versus 33%; $P < 0.001$). Despite the large percentage of black ESRD patients, there were only four black ADPKD patients (0.8%). However, the incidence rate for ESRD due to ADPKD during the 16-

TABLE 1. Occurrence of ADPKD in blacks and whites with ESRD

Patients Enrolled	N	%	ADPKD	%
ADPKD-Chattanooga ESRD program, 1975–1990				
Total	1,076			
White	718	67	49	6.8
Black	358	33	5	1.4
ADPKD-Dialysis Clinic, Inc., units in Tennessee and Atlanta (15 ESRD clinics), 1990				
Total	784			
White	298	38		
Black	486	62	4	0.8
Annual incidence				
Annual incidence per 100,000 in Hamilton Co., 1975–1990				
White, 0.47 (17 patients/224,000[a] over 16 yr)				
Black, 0.48 (4 patients/52,000[a] over 16 yr)				
Incidence ratio, black:white, 1.02				

[a] Average population for years 1970, 1980, and 1990.

yr period for the Chattanooga/Hamilton County patients was similar for blacks and whites (0.48 versus 0.47 per 100,000; ratio, 1.02).

Association of ADPKD and Sickle-Cell Trait

Seven (54%) of 13 unrelated black patients with ADPKD tested for sickle-cell trait had AS hemoglobin; the rest had AA hemoglobin. Twelve had ESRD, with six having AS hemoglobin (50%). In comparison, 6 (7.5%) of 80 black ESRD patients without ADPKD had AS hemoglobin, three (3.8%) had AC hemoglobin, and the remainder had AA hemoglobin (Figure 1). Thus, there was a higher incidence of AS in the black ADPKD patients versus black patients with other types of ESRD ($P < 0.005$). The incidence of AS hemoglobin in our black non-ADPKD ESRD patients was similar to that reported for the general black population (6 to 10%) (7,8).

Onset of ESRD in ADPKD Patients

All black ADPKD ESRD patients identified by the authors ($N = 23$) were compared with the white

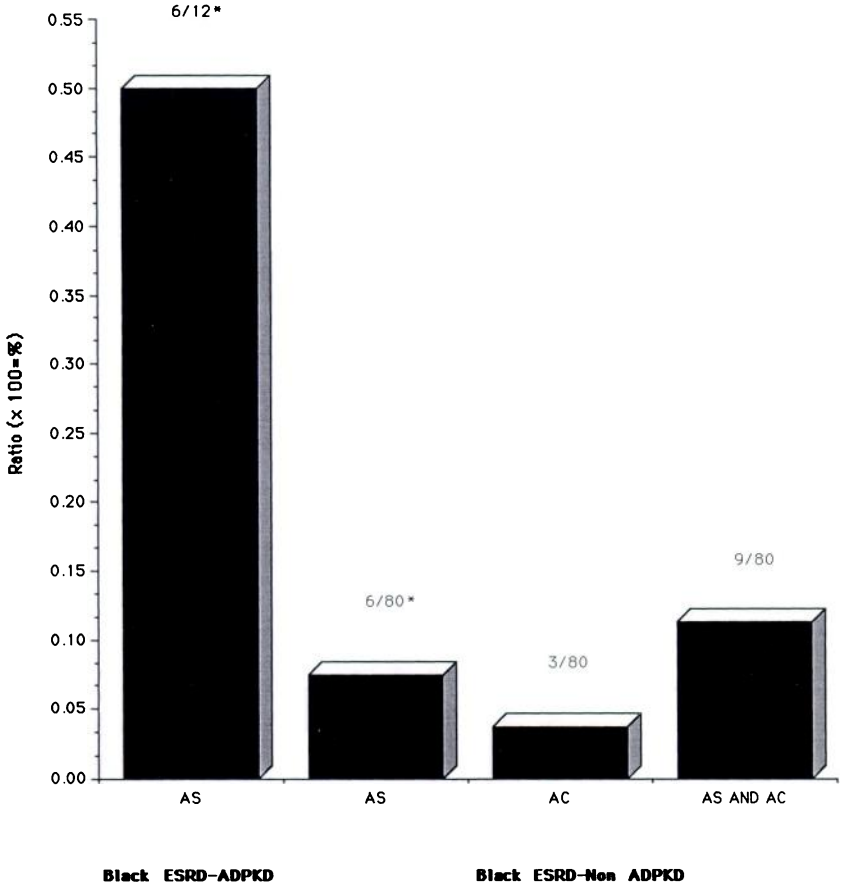

Figure 1. Occurrence of sickle-cell hemoglobin in black probands with ESRD-ADPKD versus black ESRD patients without ADPKD. * $P < 0.005$.

ADPKD ESRD patients from the Chattanooga ESRD program (N = 49). The age of onset of ESRD from ADPKD was significantly younger in the black patients than in the white patients (43.2 versus 55.4 yr; $P < 0.0001$) (Table 2). The black ADPKD patients with AS hemoglobin developed ESRD earlier than black ADPKD patients with AA hemoglobin (38.2 versus 48.1 yr; $P < 0.003$). There was no significant difference in the age at ESRD onset between black men and black women with ADPKD (41.4 versus 45.6 yr; P = not significant), but both had a significantly earlier onset than did their white counterparts (black men, 41.4 yr versus white men, 53.8 yr; $P < 0.01$; black women, 45.6 yr versus white women, 56.4 yr; $P < 0.01$). Although there was a tendency for white men to develop ESRD earlier than white women (white men, 53.8 yr versus white women, 56.4 yr; P = not significant), this was not statistically significant. Hypertension was present in the majority of patients in all groups and did not have a significant effect on the age at onset of ESRD.

DISCUSSION

Initial studies of ESRD patients in the 1970s reported that ADPKD was a less frequent cause of ESRD in blacks than in whites (1,2). The apparent low occurrence of this kidney disease in the black population in these early studies may have reflected access barriers to dialysis for blacks. Indeed, our studies show a greater percentage of black patients on dialysis now than in the 1970s. Nevertheless, this study demonstrates that, in blacks, ADPKD accounts for only 0.8 to 1.4% of the ESRD population in comparison to 6.8% in whites. This would appear to support the impression of less ADPKD ESRD in blacks. However, after correcting for the population distribution of blacks and whites, the incidence of ESRD due to ADPKD in blacks versus whites is very close, at a ratio of 1.02. This ratio is similar to those reported recently by the U.S. Renal Data System (4,5). If the ADPKD gene is less frequent in the black population, a more aggressive course of the disease in blacks could explain the similar incidence of ESRD in blacks and whites with the disease. The earlier age at onset of ESRD in blacks demonstrated in this study is supportive of this hypothesis, but data on the frequency of the ADPKD gene in blacks are lacking. In other common renal diseases leading to ESRD (hypertension, diabetes mellitus, glomerulonephritis), the incidence is approximately four times higher for blacks than whites (5). The high frequency of these other renal disorders that culminate in kidney failure dilutes the incidence of ADPKD as a cause of ESRD in blacks.

The progression of renal disease to end stage in ADPKD is influenced by a number of factors (9,10). Although the number of probands was small, a provocative aspect of this study is the observation that blacks with ADPKD had a higher frequency of sickle-cell hemoglobin. The incidence of sickle-cell trait was no higher in our non-ADPKD ESRD patients than in the general black population (7). Sickle-cell trait has not been identified to be a risk factor for the occurrence of chronic renal disease in other patient studies (8,11). The high incidence of the AS hemoglobin in the ADPKD black ESRD population could be explained by at least two mechanisms. First, the causative gene might be a non-ADPKD1 gene linked to the sickle hemoglobin mutation on chromosome 11 (12). However, the one black family with ADPKD and AS hemoglobin on whom gene linkage analysis was performed appears to have the gene on chromosome 16, as is the case in the majority of white patients with this disease (W. Kimberling, personal correspondence). The other possibility is, if the course of the kidney disease is more aggressive in the presence of AS hemoglobin compared with the effect of AS on other renal diseases, then a higher number of such patients would develop ESRD, accounting for a higher percentage of ESRD in this group of patients. Supportive of this latter hypothesis is the earlier age at onset of ESRD disease in ADPKD blacks with AS compared with those with AA hemoglobin.

In sickle-cell trait, recurrent hematuria and medullary vascular changes may occur, which could af-

TABLE 2. Comparisons of the age at ESRD for patients with ADPKD

	Black			White			*P* Value
	Age (yr)	Range	*N*	Age (yr)	Range	*N*	
All patients	43.2	28–64	23	55.4	27–79	49	<0.0001
AS hemoglobin[a]	38.2	28–50	13				
AA hemoglobin	48.1	36–57	9				
Men	41.4	28–64	13	53.8	39–71	18	<0.01
Women	45.6	35–54	10	56.4	27–79	31	<0.01

[a] $P < 0.003$, AS versus AA; one patient with hemoglobin status not known.

fect the course of ADPKD (13). Recurrent hematuria has been reported to be a poor prognostic factor in the progression of this renal disease (14). Information on the onset of gross hematuria and the frequency of such episodes in black patients with and without sickle-cell trait is needed. In addition, medullary ischemia occurs with sickling; ischemia has been implicated as a causal factor in acquired and drug-induced cystic disease and therefore may be pathogenetic in the acceleration of cystogenesis in ADPKD as well (15,16). We did not measure the degree of cystic involvement in the study, but large kidneys and more cysts are poor prognostic signs in ADPKD (9).

In a recent study of patients with sickle-cell anemia and chronic renal failure, there was reported a more frequent association with the Central African Republic (CAR) B^S-gene cluster haplotype, indicating a possible genetic factor to the development of renal failure associated with sickle-cell disease (17). One black family studied with ADPKD and sickle-cell trait had the CAR haplotype (W. Kimberling, personal correspondence).

Previous studies have demonstrated the important roles of gender and hypertension in ADPKD progression (9,10,18). Gender and hypertension were not significant factors in this study. There is no apparent reason for the lack of a gender effect. We anticipated an effect of hypertension, given the propensity of blacks for hypertension. However, hypertension in this study was determined late in the course of the disease, at entrance to dialysis, and therefore was prevalent in all patient groups and was not a discriminating factor for the age at onset of ESRD.

In summary, our study shows that black patients with ADPKD developed ESRD earlier than white patients with this disease, adding another renal disease to the list in which ESRD occurs earlier in blacks than whites. Sickle-cell trait occurred more frequently in the black ADPKD ESRD population than expected, and these patients have an even earlier onset of ESRD than black ADPKD patients with AA hemoglobin. Therefore, the presence of sickle hemoglobin should be determined in black patients with ADPKD because it is an important prognostic factor.

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