

More Adverse Renal Prognosis of Autosomal Dominant Polycystic Kidney Disease in Families With Primary Hypertension¹

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ABSTRACT

Marked variability of age at renal death is noted in autosomal dominant polycystic kidney disease (ADPKD). The hypothesis that the coexistence of primary hypertension and ADPKD within families is associated with earlier renal death was tested. Of a total of 162 ADPKD patients treated in one Austrian and three German centers, 57 probands were identified whose families provided (1) information concerning blood pressure; (2) documented presence of ADPKD (by sonography or autopsy) in one parent; and (3) age at renal death in the proband. Hypertension of the unaffected parent was defined as blood pressure above 140/90 mm Hg or antihypertensive treatment before age 60 yr. Age at renal death in the proband was defined as the start of renal replacement therapy. Median age at renal death of 23 offspring (11 male, 12 female) from families with a history of primary hypertension of the nonaffected parent was lower than that of 34 offspring (16 male, 18 female) from families without a known history of primary hypertension of the nonaffected parent, *i.e.*, 49 yr (26 to 64) versus 54 yr (28 to 82) ($P < 0.03$). The data are consistent with the notion that genetic predisposition to primary hypertension is associated with an earlier onset of terminal renal failure in families with ADPKD.

Key Words: Autosomal dominant polycystic kidney disease, primary hypertension, uremia, age at renal death

The renal prognosis of autosomal dominant polycystic kidney disease (ADPKD) is more variable than has been appreciated in the past. Considerable variability of age at renal death is found between

individuals, and to a lesser extent also between families with ADPKD. Part of such variability may be due to genetic heterogeneity. The renal prognosis is more favorable in PKD2 (or non-PKD1), which is coded on chromosome 4 (1) than in classic PKD1, which is coded on chromosome 16 (2). The gender of the affected individual also plays a role; we (3) and others found that the average age at renal death was lower in males than in females. It is unlikely, however, that these two points account for more than a fraction of total variance. Certainly, other genetic or environmental factors also play a role.

It has been very difficult to document whether hypertension is related to the rate of progression and/or age at renal death in ADPKD (4). On the one hand, Roscoe *et al.* (5) found similar age at renal death in normotensive and hypertensive patients with ADPKD. On the other hand, Gabow *et al.* (1,6) found more rapid progression, as evaluated by the reciprocal of serum creatinine, in hypertensive ADPKD patients. They also noted a relation between left ventricular mass and the rate of progression. Histologic studies document severe lesions of the afferent arterioles and interlobular arteries in end-stage ADPKD kidneys, observations that would be consistent with blood pressure-induced vascular injury (7). Resolution of the issue is confounded, however, by several factors. Because circadian blood-pressure profile is abnormal early on (8), casual blood-pressure measurements are a poor index of the blood-pressure load to target organs. The true effect of hypertension may be obscured by antihypertensive treatment. Blood pressure depends on the degree of renal dysfunction. These are only a few of the factors that confound the analysis of the role of elevated blood pressure.

We decided to tackle the problem using an entirely different methodologic approach. Genetic analysis is a powerful investigational tool. Some uncontrolled, but striking, clinical observations in ADPKD families prompted us to examine whether genetic predisposition to primary hypertension was associated with a more adverse renal prognosis. We tested the working hypothesis that age at renal death in the offspring with ADPKD was lower in families in which the parent unaffected by ADPKD had primary hypertension. In order to test this hypothesis, we screened ADPKD families in three German nephrology centers and one Austrian nephrology center. Age at renal death was assessed for offspring in families that provided information on the carrier state of parents and on the blood-pressure status of the nonaffected parent.

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PATIENTS AND METHODS

Design of the Study and Entry Criteria

In four nephrologic centers, all patients on maintenance hemodialysis with known ADPKD were contacted and gave informed consent. Entry criteria were (1) availability of information, either sonography or autopsy report, identifying the parent who was the carrier for the ADPKD trait; (2) information on blood pressure before age 60 yr in the nonaffected parent, *i.e.*, entry criteria blood pressure \geq 140/90 mm Hg or antihypertensive treatment (values measured by their private physicians); it turned out that none of the parents had blood pressure values between 140 and 160 mm Hg systolic; evidence of secondary hypertension in the nonaffected parent was specifically asked for and present in none; and (3) age at renal death in the proband. All patients were approached by one single observer (E. Stier) and interviewed. If necessary, private physicians were contacted, patient records were copied, and autopsy reports were assessed. Age at renal death was taken as the date of the first dialysis session. To evaluate whether the above patient cohorts were representative, we compared age at renal death in probands and the entire cohort of ADPKD patients (including those who did not qualify for entry into the study) who were treated in the above centers.

Patients

Proband were patients in the four dialysis centers, either on dialysis or living with a graft, for whom information on the medical history of the two parents (not necessarily alive) was available. These criteria were fulfilled by 57 of the total 162 ADPKD patients currently (as of 1993) on treatment in the four centers, comprising 10.9% of the dialysis population. The reasons to exclude 105 families were: (1) absence of definite information (by imaging or autopsy) as to which parent was the carrier of the ADPKD trait (approximately 50% of the excluded families); (2) no definite information on the circumstances of death, uremia or otherwise (approximately 30%); (3) no information on the blood pressure of the nonaffected parent (approximately 20%); and (4) a further 11 patients were excluded because of false paternity as evaluated by interview. These reasons for exclusion concerned 94 families. These 94 censored patients were similar to the remaining 57 probands who were included for the definite analysis (see Table 1) with respect to gender, age, and duration of dialysis.

No family was excluded because hypertension occurred after age 60 in the nonaffected parent. In the 57 families selected for final analysis, 53 affected parents had come to end-stage renal failure, 3 had been killed by war events, and 1 had died from hepatic cirrhosis. The 57 ADPKD patients

who were the probands came from 57 different families. Twenty-nine patients were on dialysis, and 28 lived with a graft.

Ancillary Information

Ninety percent of the probands were hypertensive (blood pressure \geq 140/90 mm Hg or antihypertensive treatment) at the start of renal replacement therapy (at least 10 measurements). Seven of the 23 offspring of hypertensive and 10 of the 34 offspring of normotensive patients were smokers.

Proband were interviewed concerning the presence of cerebral aneurysms (one case *versus* no cases in the censored ADPKD patients), episodes of macrohematuria (3.5 *versus* 4.2%), upper urinary tract infection (7 *versus* 7.2%), renal stones (9 *versus* 4.2%), myocardial infarction (7 *versus* 10%), stroke (3.5 *versus* 6%), and other serious coexistent diseases, *e.g.*, surgery for diverticulosis (5.3 *versus* 8%). Body mass index was below 27 kg/m² in all individuals: mean, 26.1 \pm 2.68 in noncensored and 25.3 \pm 3.51 in censored patients.

Statistics

Data are presented as median and range. Comparison of age at renal death between the two groups was carried out by the use of Wilcoxon's test for random samples. Testing for Gaussian distribution was performed by use of the Shapiro Wilk test. PROC univariate from SAS 6.08 was used to calculate descriptive analysis. Life table analysis was performed with PROC LifeReg with Kaplan Meier option. Cox regression analysis was performed to verify the independent effect of gender and family history of hypertension, as well as their potential interaction, with PROC PHREG (from SAS Statistics Package Rel 6.08; SAS Institute, Cary, NC).

RESULTS

Characteristics of Proband and Their Parents

Proband with ADPKD and censored ADPKD patients are compared in Table 1. The proportion of probands suffering from urologic problems potentially causing renal failure was comparable in the two populations (see above).

Urologic problems were similarly frequent in probands from normotensive and hypertensive families, with the exception of urinary tract infection. A history of renal stones was present in 5 of 57 probands, of whom 2 had hypertensive and 3 had normotensive nonaffected parents. A history of upper urinary-tract infection was present in 4 of 57 probands, all 4 of whom had normotensive nonaffected parents. Seven of 10 female probands with a hypertensive nonaffected parent had pregnancies (median number of births, 2; range, 1–4); in 2 patients, hypertension was present during pregnancy. Twelve of the 17 female probands with a normotensive nonaffected parent had pregnancies (median number of births, 2; range, 1–5); in four patients, hypertension was present during pregnancy.

Of the 57 parents with documented absence of ADPKD, 27 were mothers and 30 were fathers. At the time of the study, 19 of 27 of the mothers and 11 of 30 of the fathers were alive, with an average age of 71 \pm

TABLE 1. Characteristics of patients with ADPKD fulfilling the entry criteria (proband) or patients censored

Parameter	Proband (N = 57)	Censored (N = 94)
Gender	30 male/ 27 female	50 male/ 44 female
Age (yr)	56.5 \pm 9.43	55.2 \pm 13.8
Duration of Dialysis (yr)	6.9 \pm 3.8	7.4 \pm 4.4
Age at Renal Death (yr)	50.76 \pm 9.15	50.21 \pm 9.13

15 yr. In the deceased parents, death had occurred on average 22.5 yr ago (5.5 to 64.5) in the 19 fathers and 5.9 yr ago (2.5 to 41.5) in the 8 mothers. In 16 of 23 nonaffected parents with hypertension, more detailed information on blood pressure was available. In all, blood pressure was above 160 mm Hg systolic and isolated systolic hypertension was not present. The onset of hypertension had occurred before age 40 yr in 1 parent, between age 40 and 50 in 4 parents, and between age 50 and 60 in 11 parents. Hypertension tended to occur at younger ages in the offspring of hypertensive nonaffected parents (36 yr; 17 to 55) than in offspring of normotensive nonaffected parents (42.8 yr; 22 to 70), but the difference was not statistically significant ($P > 0.05$). In the 31 normotensive nonaffected parents who had died, age at death was 68.9 yr (33 to 88); in the 19 hypertensive nonaffected parents who had died, age at death was 65 yr (40 to 89).

Analysis of the causes of death showed that 13 of 27 nonaffected parents died from cardiovascular causes and 14 of 27 died from noncardiovascular causes (including war fatalities). Of the 3 hypertensive nonaffected fathers who had died, all had died from cardiovascular causes, but of the 16 normotensive nonaffected fathers, only 9 died from cardiovascular causes (= 56%); among the mothers ($N = 8$), figures are too small for meaningful analysis. The higher proportion of cardiovascular deaths among the nonaffected parents defined as hypertensive nevertheless would be in line with what one would expect in a hypertensive population.

Relation of Parent Blood Pressure and Age at Renal Death in Offspring

The legend to Figure 1 indicates that age at renal death was significantly lower in male probands, suggesting that gender is a confounding variable. As shown in Figure 1 and Table 2, age at renal death was significantly ($P < 0.03$) lower in probands whose nonaffected parent was hypertensive than in those whose nonaffected parent was normotensive. Figure 1 shows, by Kaplan Meier survival analysis, the comparison of age at renal death between probands whose nonaffected parent was hypertensive and those whose nonaffected parent was normotensive. Because gender is an important confounder, we emphasize that of the probands whose nonaffected parent was hypertensive, 11 were male and 12 female; of the probands whose nonaffected parent was normotensive, 16 were male and 18 were female. Figure 1b shows earlier age at renal death in male as well as female probands with ADPKD who had a hypertensive parent compared with probands who had a normotensive parent. Cox regression analysis also excluded gender as a significant confounder: testing each variable, *i.e.*, gender and family history of hypertension, using the univariate model showed that both variables were highly significant ($P < 0.05$). By use of the multivariate model in

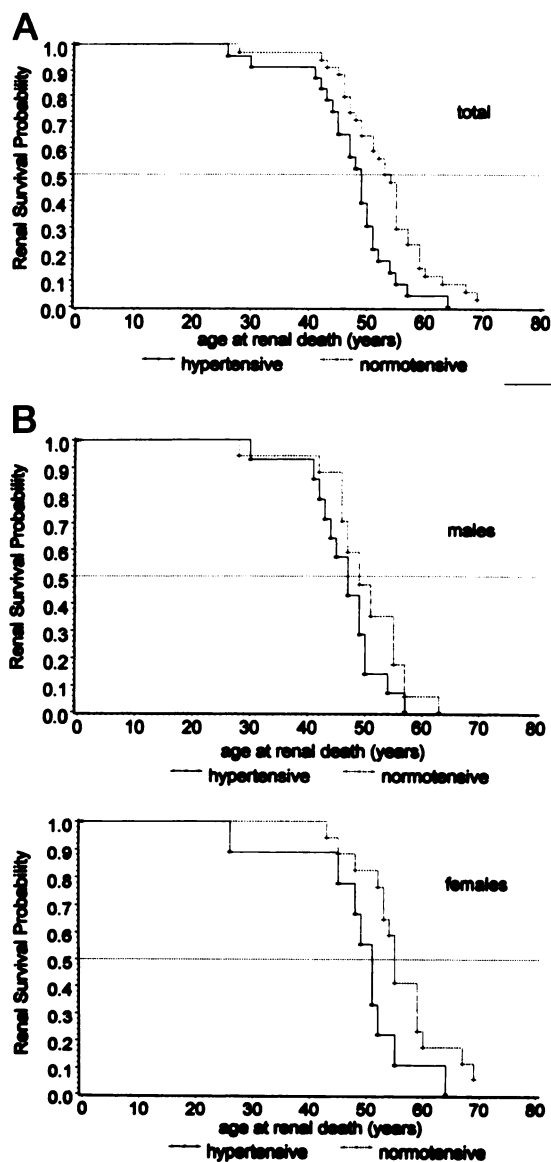


Figure 1. Renal survival probability, *i.e.*, survival without renal replacement therapy, in probands with ADPKD according to presence or absence of hypertension in the nonaffected parent. (A) All probands ($N = 57$). (B) Renal survival probability in male ($N = 27$) and female ($N = 30$) probands. Median age at renal death: 48 yr (28–63) in males ($N = 30$) and 53 yr (26–82) in females ($N = 27$).

PROC PHREG (option stepwise), it was shown that both variables were independent.

To exclude a potential effect of imprinting, we compared age at renal death in probands whose disease was transmitted from the father and from the mother, respectively (Figure 2). In this limited cohort, there was no significant difference ($P = 0.16$).

To exclude an artifact from anticipation, we also explored whether a systematic trend was present for renal death to occur earlier in the *f1* generation. Of the

TABLE 2. Age at renal death according to blood pressure in the nonaffected parent

BP Status in the Nonaffected Parent	Age at Renal Death of Propositus (yr)		
	All	Sons	Daughters
Hypertensive (N = 23)	49 (26-64) (N = 23)	46.4 (30-57) (N = 11)	48 (26-64) (N = 12)
Normotensive (N = 34)	54 (28-82) ^a (N = 34)	49.6 (28-63) (N = 16)	56.6 (43-82) (N = 18)

^a P = 0.03.

57 parents with ADPKD, 53 had reached end-stage renal failure. In the 53 parent/offspring pairs, the difference of age at renal death between parent and offspring was symmetrically distributed around the difference zero. Distribution of the differences was Gaussian according to the Shapiro Wilk test.

DISCUSSION

This study documents that a significant difference of age at renal death exists between propositi with ADPKD, depending on whether the nonaffected parent is normotensive or hypertensive. The difference is not explained by a confounding effect of gender. The observation is consistent with the notion that the presence of the genetic trait for primary hypertension is responsible for one of the following: (1) that loss of renal function starts at an earlier age; (2) that the progression of established renal failure is accelerated; and (3), or both. Our data do not permit us to distinguish between these possibilities.

For this analysis, we equate hypertension of the nonaffected parent with a higher genetic risk for primary hypertension in the offspring. From family studies (9,10), it is well known that only a proportion of the offspring of parents with primary hypertension actually develop hypertension in early adult life. This fact will reduce the difference for age at renal death by including genetically normotensive individuals in the group of offspring of hypertensive patients. This factor would operate against the working hypothesis that hypertension in the nonaffected parent causes earlier renal death in the offspring with ADPKD. It is therefore particularly remarkable that a difference was observed in view of the limited power of the study because the sample size was small for logistic reasons. Consequently, the above difference of age at renal death must be considered a minimal estimate. Unfortunately, direct identification of the genetic trait for primary hypertension is currently not possible.

A number of biostatistical artefacts must be discussed that may affect interpretation of the results. No information was available as to whether the above families had PKD1 or PKD2. This point is of importance, because renal prognosis is more benign in PKD2 families (see Ref. 12). There is no *a priori* reason, however, why the ratio of PKD1 to PKD2 should have

been different in hypertensive and normotensive families.

The proportion of parents who did not suffer from ADPKD and who had been hypertensive at age 60 yr, *i.e.*, 40%, is high. It is close to the upper 95% confidence interval for the prevalence of true hypertension in the city of Munich for individuals at age 59 yr or more, *i.e.*, 38.7% in males and 42.1% in females. In the deceased fathers who had died at an average age of 48.5 yr, 3 of 19, *i.e.*, 15.8%, were hypertensive, again in reasonable agreement with the figures of Stieber *et al.* (11). Nevertheless, the possibility of selection bias exists. If renal prognosis is more favorable in families without primary hypertension, one would anticipate that at a given age, the risk for offspring of normotensive families to reach end-stage renal failure is less than for offspring of hypertensive families. If the subjects did not develop end-stage renal failure, they would not have been recruited for this study.

Another source of selection bias might be higher cardiovascular mortality in the offspring of hypertensive parents. Selective nonrenal loss of offspring from hypertensive families or, conversely, preferential survival of nonhypertensive subjects should operate against the above working hypothesis, however.

One further potential source of bias relates to the fact that the propositi were not an inception cohort, *i.e.*, patients beginning renal replacement therapy, but a cohort of all patients on renal replacement therapy. Again, patients with ADPKD who had started treatment in the four centers, but who had died before propositi were recruited, might introduce a bias. We do not have direct information on this point, but again, one would assume that early death on renal replacement therapy would be more likely in individuals with a family history of hypertension. Nevertheless, this and the above points certainly represent the limitations of the study, of which we are fully aware.

Another issue is whether the propositi are truly an unbiased sample of the entire ADPKD patient population of the respective centers. At least with respect to age at renal death, ratio of genders, and presence of urologic complications with potential effect on renal prognosis, the propositi for whom we happened to have complete family information were similar to the ADPKD patients who were excluded, *i.e.*, censored, because of incomplete information on parents. Although blood group and HLA group determinations were not done systematically, false paternity was confirmed by interview in at least 6.8%. This figure is remarkably close to the proportion with false paternity found in a local sample in Heidelberg (unpublished data), where we did genomic analysis of the major histocompatibility complex II locus in a study on families with immunoglobulin A glomerulonephritis. False paternity was an exclusion criterion in the above study.

Urologic complications, particularly episodes of macrohematuria and urinary tract infection, are predictors of an adverse renal prognosis (6). The preva-

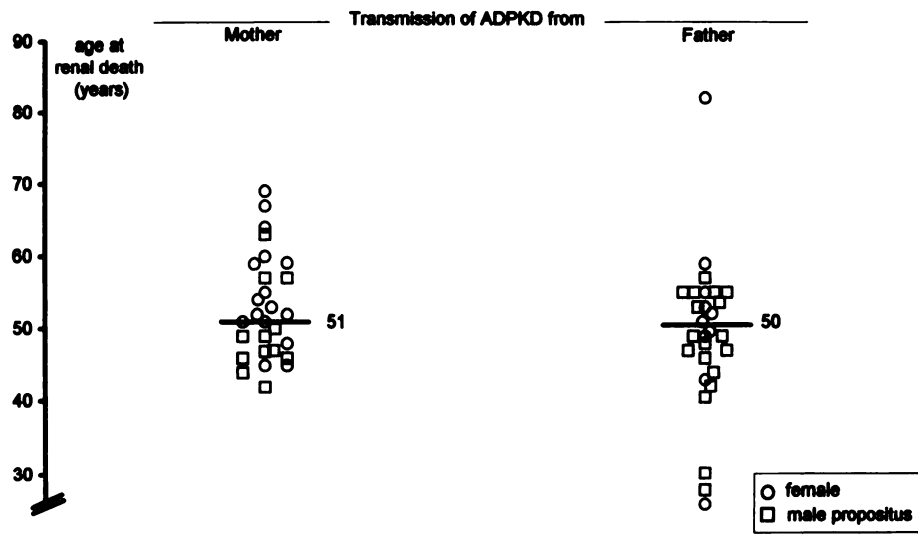


Figure 2. Age at renal death according to whether the transmission of the ADPKD trait occurred from the father or from the mother. No significant difference was found ($P < 0.16$).

lence was remarkably low in this patient sample and was comparable in offspring from normotensive and hypertensive families.

Recently, two observations have been reported that may potentially affect this type of analysis. It has been suggested that imprinting caused by postmeiotic modification of genomic DNA may affect renal prognosis; a more unfavorable prognosis was found when the disease is transmitted from the mother (12). We observed no significant difference of age at renal death according to the gender of the transmitting parent in this sample of limited size. Furthermore, it has been recently reported (13) that anticipation of age at renal death occurs in some ADPKD families, suggesting the presence of unstable DNA. This would obviously have implications for data analysis, but evidence for this was not noted in the above sample.

The relation between hypertension and progression of renal failure in ADPKD is complex, as discussed above (4–6). The conclusion of Gabow *et al.* (6) that blood pressure is related to renal prognosis is supported by the independent information resulting from this study. Indeed, if genetic hypertension initiates or accelerates loss of renal function in patients with ADPKD, it is unlikely that hypertension is merely a marker of, or a result from, renal dysfunction. The latter interpretation could not be definitely excluded in past cross-sectional and retrospective studies (4). Our observation is more in line with the notion that hypertension is a player in progression. More severe vascular damage, as shown by the histology of the kidney in ADPKD patients with end-stage renal failure (7), would provide a plausible mechanism, but alternative possibilities are of course not excluded. Nevertheless, the limitations of the study, with regard to sample size and potential recruitment bias, necessitate independent confirmation of the results in other

studies, before the above conclusions can be considered as definitely proved.

The results of intervention trials with intensified antihypertensive treatment late in the course of renal failure in patients with ADPKD have remained disappointing (14). The present observation provides a further incentive, however, for controlled prospective trials on early antihypertensive intervention in patients with ADPKD. Such a study was recently launched by the Concerted Action Toward Prevention of Polycystic Kidney Disease in Europe.

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