Artificial
Organs

Adult Polycystic Kidney Disease: Who Needs Hospital Follow-Up?

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Abstract: Clinical data from 120 adult patients with genetically undifferentiated polycystic kidney disease who had been followed up for more than 3 months (range 3–172) were reviewed in order to try to identify clinical indicators that might predict deterioration in renal function. They were split into two groups dependent on whether annualized fall in estimated glomerular filtration rate (ΔeGFR mL/min/1.73 m^2/year) was statistically significant or not. Only 26 patients (22%) had a statistically significantly decreasing ΔeGFR with a median decrease of –2.6 mL/min/1.73 m^2/year (range –6.2 to –0.7). There was no difference in initial age, gender, or racial distributions between the groups or in initial eGFR. Follow-up was longer (median 86, range 23–172 months vs. 46, range 3–161 months; P = 0.002) and initial blood pressure values tended to be lower (with mean systolic values of 128 vs. 148 mm Hg; P = 0.02) in the group with statistically significant fall in ΔeGFR, but this trend failed to achieve an a priori level of statistical significance. However, the proportion of patients with initial systolic blood pressure ≤144 developing a statistically significant fall in ΔeGFR was 0.26 (95% confidence interval = 0.13 to 0.45). No differences were found in initial hemoglobin or cholesterol concentrations. Overall, the annualized rate of decrease in eGFR tended to be greater in those with the higher initial eGFR (P = 0.04), but correlation was poor (rho^2 = 0.04) and failed to achieve an a priori level of statistical significance. No statistically significant correlation was found between ΔeGFR and any other variable. Only those patients with polycystic kidney disease with a statistically significant annualized decrease in eGFR may need to be referred for hospital follow-up in the renal clinic. This simple selection would reduce referrals by 78%.
Key Words: Glomerular filtration rate—Adult polycystic kidney disease—Blood pressure—Follow-up.

Adult polycystic kidney disease (APKD) is one of the most common genetic disorders associated with a defect in a single gene and, at the same time, one of the most common causes of chronic renal failure. Any symptoms usually develop in the third or fourth decade, if at all. By the age of 60 years, approximately half of patients require renal replacement therapy (1). However, renal impairment may occur earlier or later and it is not extremely rare to find polycystic kidneys at postmortem examination of elderly subjects who have died from other causes. At the same time, the rate of deterioration of renal function in APKD, resulting in renal failure, not only varies between affected members of different families but also between different members of the same family. In some individuals, kidney cysts are present in early childhood and progress to established renal failure before the age of 40, whereas renal function remains unimpaired throughout life in others. Several general factors, such as gender, germ-line mutations, modifier genes, and epigenetic factors, affect disease progression with respect to cyst growth, interstitial inflammation, and progressive fibrosis (2–4). In view of these observations, it not easy to predict outcome in the individual patient with APKD so much so that some clinicians declare that this is impossible (5).

In order to treat patients with APKD where development of established renal failure is only a possibility, it would be helpful to identify simple predictors that discriminate between those more likely to retain adequate renal function and those more likely to develop progressive renal impairment terminating in a need for renal replacement therapy. This is

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particularly important in those renal units where an ever-increasing number of referrals make it essential to concentrate the expertise of specialists on those patients most at risk so that any interventions likely to improve prognosis are given to those most likely to benefit, and effort is not wasted on those who already have a good prognosis.

The aim of this study was retrospectively to identify those patients with APKD who developed progressive loss of renal function and those who did not by reviewing a registry of patients with APKD being monitored and treated in a dedicated clinic. Candidate clinical features at presentation were then compared to determine if significant differences existed that would permit prediction of outcomes. In this way, factors that might affect clinical course should be evident such that it should be possible to determine those who really need referral for hospital follow-up.

PATIENTS AND METHODS

Data collection

The clinical data of 184 patients with APKD attending a dedicated clinic were reviewed. Of these, 120 of them satisfied the criteria for inclusion in this study. Patients excluded were less than 18 years of age or had been followed up for a period of less than 3 months or had less than four data points to calculate change in estimated glomerular filtration rate with time (ΔeGFR, mL/min/1.73 m^2/year). In each case, gender and age were recorded. Patients were classified by race into white, black, Indo-Asian, and oriental. Seated systemic arterial blood pressure (systolic, diastolic, and mean), recorded at the time of first clinic attendance, was noted, as was the result of initial laboratory estimation of hemoglobin, cholesterol, and creatinine concentrations.

Statistical methods

In each case, estimated glomerular filtration rate (eGFR) was calculated using the four-variable form of the Modification of Diet in Renal Disease (MDRD) formula. Using the same method, the eGFR at successive time points during follow-up of each patient was calculated. This enabled estimation of the annual rate of change (ΔeGFR) of renal function employing linear regression. The patients were then classified into those who had a statistically significant ($P < 0.05$) average rate of deterioration in renal function (–ΔeGFR) and those who did not. For each of these groups, the Kolmgorov–Smirnoff test was employed to test whether continuous variables were distributed in a Gaussian fashion. In the case of those that were normally distributed, means and standard deviations were calculated. In the case of those that were not normally distributed, median, interquartile range, and ranges were calculated. In the case of continuous variables that were normally distributed and where variances were homoscedastic, mean values were compared between the two groups using Student's *t*-test for independent samples. In the case of continuous variables that were normally distributed but where variances were heteroscedastic or where continuous variables were not normally distributed, median values were compared using the Mann–Whitney *U*-test. Racial distributions were compared using contingency table analysis by χ^2-test or Fisher's exact test as appropriate. In the case of individual calculations to estimate ΔeGFR, correlation coefficients were considered to be statistically significant when $P < 0.05$. In the case of multiple comparisons of patient characteristics between groups, differences were considered to be statistically significant when $P < 0.01$. As the distribution of annual change in eGFR was not normally distributed, rank correlation was attempted between this and other clinical variables, and, as multiple comparisons were involved, correlations were considered to be statistically significant when $P < 0.01$.

RESULTS

Duration of follow-up

The median duration of follow-up of the 120 patients included in the study was 52 months (range 3–172 months).

Characteristics of patients

No patients of oriental origin were represented. Characteristics of patients are shown in Table 1, both for the group as a whole and following subdivision dependent on whether the estimated annual fall in ΔeGFR (mL/min/1.73 m^2/year) was statistically significant. No statistically significant differences in distribution by gender or race were found between the groups. Median duration of follow-up was greater (86 months) in those with progressive loss of renal function when compared with that (46 months) of those with no progressive loss of renal function.

Annual rate of change in renal function

The distribution of ΔeGFR values for the whole group is shown in Fig. 1, where the median value was –0.8 mL/min/1.73 m^2/year with a maximum of +23.9

TABLE 1. *Characteristics of patients. Patients were subsequently split into two groups: those without and those with statistically significant annual deterioration in eGFR whose characteristics were then compared statistically*

Variable (units)	All patients	Those *without* a statistically significant annual deterioration in eGFR (= ΔeGFR)	Those *with* a statistically significant annual deterioration in eGFR (= ΔeGFR)	*P* value
Number (*n*)	120	94 (78%)	26 (22%)	—
Median ΔeGFR [range] (mL/min/1.73 m^2/year)	–0.8 [–17.25 to +23.9]	–0.2 [–17.25 to +23.9]	–2.6 [–6.2 to –0.7]	$P < 0.0001$
Male/Female	47/73	33/61	14/12	$P = 0.26$
Mean age ± SD (y)	36.7 ± 12.7	36.6 ± 13.0	36.7 ± 11.6	$P = 0.97$
Race: White/Black/Asian (*n*)	103/7/10	80/6/8	23/1/2	$P = 0.32$
Median duration of follow-up [range] (months)	58 [3 to 172]	46 [3 to 161]	86 [23 to 172]	$P = 0.002$
Mean initial Hb ± SD (g/dL)	13.6 ± 1.5	13.7 ± 1.4	13.4 ± 1.7	$P = 0.42$
Mean initial cholesterol ± SD (mM/L)	4.86 ± 1.1	4.88 ± 1.1	4.81 ± 1.0	$P = 0.84$
Mean initial eGFR ± SD (mL/min/1.73 m^2)	74.2 ± 18.2	73.2 ± 17.4	78.0 ± 21.0	$P = 0.25$
Mean systolic BP ± SD (mm Hg)	146 ± 21	148 ± 21	128 ± 11	$P = 0.02$
Mean diastolic BP ± SD (mm Hg)	82 ± 11	82 ± 12	78 ± 5	$P = 0.07$
Mean MAP ± SD (mm Hg)	104 ± 13	105 ± 13	95 ± 5	$P = 0.04$

BP, blood pressure; MAP, mean arterial pressure.

(improving renal function) and minimum of –17.25 mL/min/1.73 m^2/year (deteriorating renal function). Following subdivision, there was a 10-fold difference in median ΔeGFR between the groups with values of –0.2 and –2.6 mL/min/1.73 m^2/year for those without and those with progressive loss, respectively. Those with progressive loss were the minority constituting 22% of all patients.

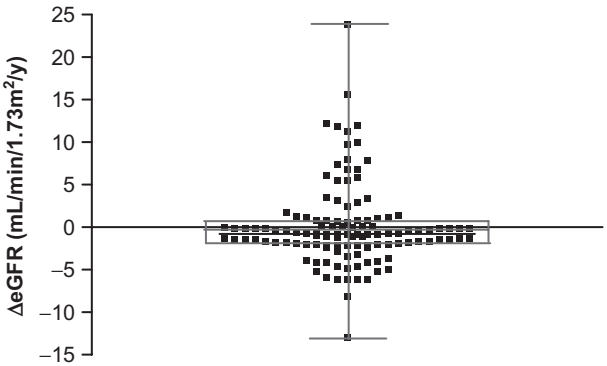

FIG. 1. Distribution of ΔeGFR for all patients with APKD: median = –0.8 mL/min/1.73 m^2/year (interquartile range = –2.1–0.8; range = –17.2–23.9).

Clinical and laboratory variables

No statistically significant differences in initial hemoglobin or cholesterol concentrations or eGFR values were found between the groups. There was a trend for initial systolic, diastolic, and mean arterial blood pressure values to be lower in the group of patients destined to develop deteriorating renal function, but differences failed to achieve a priori levels of statistical significance.

Lack of correlation between ΔeGFR and other variables

As ΔeGFR was not normally distributed, rank correlations were sought between ΔeGFR and other variables (with the exception of patient's age as this variable is used to calculate eGFR) and the results are shown in Table 2. There was a trend for higher

TABLE 2. *Rank correlations between ΔeGFR and other variables*

Variable (units)	Number of paired values	Spearman's rho	Probability
Duration of follow-up (months)	120	–0.07	$P = 0.48$
Initial eGFR (mL/min/1.73 m^2)	120	–0.19	$P = 0.04$
Initial Hb (g/dL)	100	0.09	$P = 0.35$
Initial cholesterol (mM/L)	53	0.05	$P = 0.74$
Initial PTH (pg/mL)	7	0.22	—
Initial systolic BP (mm Hg)	55	0.11	$P = 0.44$
Initial diastolic BP (mm Hg)	55	0.12	$P = 0.39$
Initial MAP (mm Hg)	55	0.18	$P = 0.18$

BP, blood pressure; MAP, mean arterial pressure; PTH, parathormone.

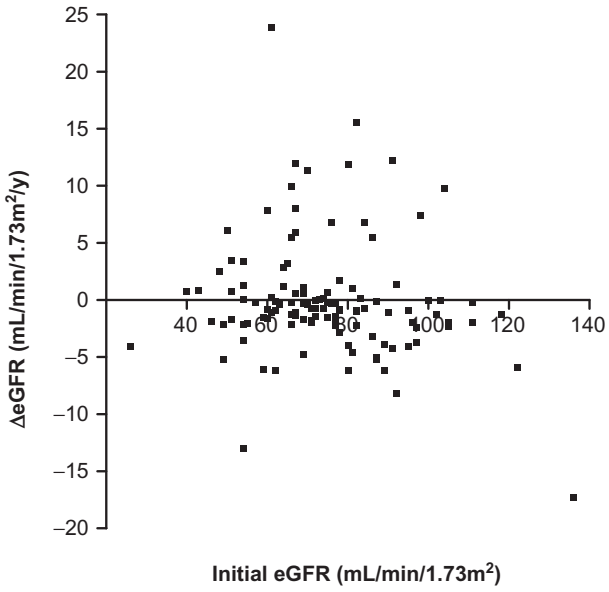

FIG. 2. ΔeGFR (mL/min/1.73 m^2/year) versus initial eGFR (mL/min/1.73 m^2). Spearman's rho = –0.19, $P = 0.04$.

initial eGFR values to be associated with faster deterioration (–ΔeGFR) in subsequent renal function (shown in Fig. 2), but the correlation coefficient failed to achieve a priori levels of statistical significance.

DISCUSSION

Previous studies

Despite a high prevalence and incidence of APKD, major gaps remain in our understanding of the natural history of this disease. Dalgaard's classic monograph has long served as a major source of information about APKD (6). Although Dalgaard reported on a large number of patients, the study was retrospective, with one-third of the patients diagnosed at autopsy. Since then, many studies of patients with APKD have been published, but have been limited by relatively small numbers of patients. The last study of the rate of deterioration in polycystic kidney disease was published nearly 20 years ago (5).

Rarity of APKD in non-white races

The results from the study of our patients with APKD patients show that there was no difference in initial age, gender, or racial distribution or in initial eGFR between the groups destined to develop deteriorating renal function and those that would not develop this. The vast majority of our patients were white, but the population of the West Midlands is notably multiracial in comparison with other parts of the UK. According to the Office of National Statistics, 17% of the population of the West Midlands classified themselves as non-white British with Birmingham having the highest concentration in this region, comprising 38% of its population. With this in mind, blacks constituted just 1.7% of the study group, an observation which supports another report that suggests that this disease is exceptional in Afro-Caribbean patients with a prevalence of APKD of 1:250 (7). Adult polycystic disease was significantly less common in Indo-Asians when compared to whites and blacks in the West Midlands even 17 years ago (8).

Lack of influence of age at presentation on subsequent progression of APKD

In 22% of patients, eGFR subsequently decreased with statistical significance. In this group, age at the time of presentation did not seem to predict subsequent deterioration. This is interesting when comparison
is made with the ages of patients enrolled in the MDRD study. In this study, the age of patients with APKD (mainly in the 40–60-year age group) was very similar to patients with other causes of chronic progressive kidney disease (9). Hence, although all patients with APKD have an abnormal polycystin gene associated with it, age does not seem to influence the age of onset of renal insufficiency which can vary widely from 3 to 80 years of age.

Comparability of ΔeGFR values with other studies

An average decrease in GFR in patients without hypertension and chronic kidney disease ranges from 2 to 3 mL/min/year (9). A previous study of patients with APKD with deteriorating renal function suggested that disease progression is constant and similar to most other patients with chronic kidney disease with GFR decreasing by approximately 4–5 mL/min/year (1). In our study population with significantly decreasing renal function and baseline GFR of 78 mL/min/1.73 m^2, median decrease in GFR was just 2.6 mL/min/1.73 m^2/year but, with a range of –0.7 to –6.7 mL/min/1.73 m^2/year, this seems comparable with other studies. The figures used in the present study are based on the use of the increasingly accepted MDRD formula, which corrects for surface area (reducing uncorrected GFR values). However, rates of change should be the same whatever method of GFR estimation is used, provided it correlates accurately with true change of GFR. When GFR is assessed on the basis of creatinine clearance, a measure that gives a more optimistic assessment of renal function as "true" GFR assessed by "gold stan-

dard" methods falls, a slower rate of terminal decline in renal function may be apparent. Thus, those patients with statistically significant falls in eGFR in the present study may be less severely affected than those in other studies and this could account for a lack of correlation with other clinical and laboratory variables that might otherwise indicate an adverse prognosis.

In view of its increasing acceptance, use of the MDRD formula for estimating GFR and its change should permit more ready comparison between different studies of the decline of renal function with time without need for speculative allowances for any incongruities related to methods of assessment. Overall median change in GFR in our study population was only 0.8 mL/min/1.73 m^2/year and included some patients with apparently improving renal function. In general, the rate of decline of renal function among APKD patients in previous studies has varied from 1.1 to 7 mL/min per year (10,11), but these may have excluded less severely affected patients. The advent of high-quality ultrasonography now permits earlier yet reliable diagnosis, and estimates of decline in such patients may be slower at an earlier stage. The earlier studies were largely retrospective, where a higher proportion of patients might have been diagnosed by less sensitive methods than ultrasound. Renal function, assessed using less sensitive measures such as serum creatinine and creatinine clearance, may have been more advanced. They also included patients who did not have a documented baseline decrease in renal function. The inclusion in our study of asymptomatic participants diagnosed earlier and a subset of participants whose renal function may have remained virtually stable could have contributed greatly to the overall variability in the rates of change in renal function.

Influence of blood pressure

In patients destined to develop significant renal deterioration during the follow-up period, initial average mean arterial pressure was 95 mm Hg. This near-normal value did not prevent progressive loss of renal function. The average mean arterial pressure in all study patients was 104 mm Hg. No prospective studies of blood pressure control over many years in patients with APKD have been found and this has not been studied here. Widely varying rates of hypertension (13–81%) have been reported in patients with APKD. However, this variability may have been the result of differing degrees of renal insufficiency in the populations studied (12–14). Our study population with subsequent significant deterioration of renal function had an initial mean eGFR of 78 mL/min/1.73 m^2, and this better level of renal function could be one reason to account for better blood pressure levels in this group of patients. However, this is probably not the only reason. It is well known that the pathogenesis of hypertension in patients with APKD, which most frequently occurs before any clinically relevant loss of renal function, is multifactorial (15). The relative roles of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, sodium retention, and endothelial dysfunction in the hypertension of APKD cannot be ascertained with certainty (2). It is of interest, however, that patients who have APKD with normal blood pressure exhibit increased total body sodium as compared with unaffected siblings, thus suggesting an early role of the RAAS (12). Although there is substantial published evidence of the importance of the rate of increase in renal volume and activation of the RAAS with the occurrence of hypertension in APKD, the beneficial effect of achieving lower blood pressure (120/80 mm Hg) and inhibition of the RAAS has been confined solely to reversal of left ventricular hypertrophy. No prospective, adequately powered, randomized study is available to support or refute a beneficial effect of inhibition of the RAAS to slow the progression of the APKD (16).

The extent to which tight blood pressure control delays the progression of renal failure in our patients must be speculative. The studies available do not show any advantageous effect of good blood pressure control over a period of 2 years in patients with APKD and deteriorating renal function (9). On the other hand, the extent to which a long-standing modest elevation in blood pressure contributes to generalized vascular disease is unclear. Nevertheless, the potential benefits of good blood pressure control in delaying progression of vascular and particularly coronary artery disease should not be forgotten.

Patients with stable renal function

In those patients with rather stable renal function over the follow-up period, no significant correlation was found between age of patients, duration of follow-up, and ΔeGFR. That means that patients, who for unknown reasons do not develop significant decline in their renal function for a period of 5 years, probably do not usually need the care of a specialist. Any intervention may only have an impact when GFR starts to decline significantly. According to our data, only those patients with polycystic kidney disease with a statistically significant annualized decrease in eGFR need to be referred for hospital follow-up. This simple selection would reduce referrals by 78%.

Etiology

This study has not shed much light on the factors that may affect disease progression in patients with APKD. However, research in animals, although not directly applicable to humans (17), has suggested a number of possibilities. These include the type of gene mutation, modifying genes, environmental factors, genes that encode proteins involved in cyst growth, genes involved in hypertension, and genes that modify polycystic kidney disease in mice. These possibilities indicate the scale of investigations still required if beneficial therapeutic interventions for this common cause of renal disease are to be identified (18).

CONCLUSION

Our study population of patients with adult polycystic kidney disease was mainly Caucasian. Only one in every five patients had significant deterioration of renal function during the follow-up period. Initial age, glomerular filtration rate, and blood pressure did not predict outcome. It seems that other contributing factors such as germ-line mutations, modifier genes, and epigenetic factors may be of greater importance in affecting cyst growth, interstitial inflammation, progressive fibrosis, and other factors that adversely affect functional deterioration.

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