Kidney International, Vol. 44 (1993), pp. 1101–1108

Autosomal dominant polycystic kidney disease in Toronto

JANET M. ROSCOE, JANE E. BRISSENDEN, E. ALEXANDER WILLIAMS, ANNE L. CHERY, and MEL SILVERMAN

Division of Nephrology, The Wellesley Hospital; Toronto Region Dialysis Registry, Multiple Organ Retrival and Exchange—Toronto Region; and Division of Nephrology, The Toronto Hospital, General Division, Toronto, Ontario, Canada

Autosomal dominant polycystic kidney disease in Toronto. This study describes the Toronto, Ontario experience with autosomal dominant polycystic kidney disease (ADPKD). Patients were divided into three groups: Group 1, 19 families studied with genetic markers; Group 2, 80 pre-dialysis ADPKD patients followed by Toronto nephrologists in whom the incidence of non-renal complications and the mean age of onset of symptomatology is documented; Group 3, 4,449 individuals who entered end-stage renal failure (ESRF) in the Toronto region between the years 1981 and 1992, 320 with ADPKD and 4129 with other diseases. In this third group age of onset of ESRF, frequency, age and cause of death is compared between ADPKD and non-ADPKD. ADPKD caused by a gene different from that linked to chromosome 16 short-arm probes occurred at a frequency of between 8 and 17%. Incidence of hepatic cysts in ADPKD was similar to that of previous series, other organ involvement was underdiagnosed without deliberate screening, and incidence of symptomatic intracranial aneurysm was 1.25%. A 5% excess of patients with ADPKD died of cerebro-vascular accident. Years of survival after ESRF measured by life table analysis was significantly greater for ADPKD patients than for non-ADPKD patients. A high frequency of death due to infection still exists in ADPKD despite the reduction of invasive procedures in diagnosis and treatment, and despite the presumably improved recent methods of managing infection. The average age of onset of ESRF has been delayed by over six years, and average age of death of ADPKD patients at 63.9 years-old by 12.4 years since 1960.

Autosomal dominant polycystic kidney disease (ADPKD) is inherited as a Mendelian autosomal dominant trait, with the children of affected individuals having a 50% chance of inheriting the gene associated with the condition. This very common illness is estimated to affect 1 in 400 to 1 in 1,000 people, comprising as many as 600,000 individuals in the United States [1, 2]. The gene has an apparent mutation rate of 6.5×10^{-5} to 10×10^{-5} [3]. In Ontario, Canada, with a population approaching 3,900,000 people, 3,900 persons would be expected to have ADPKD. An estimated 50% of these will progress to end-stage renal failure (ESRF) and will contribute approximately 9% of new ESRF patients per year.

Patients with ADPKD are at risk of developing other manifestations as well as ESRF. These include hypertension, urinary tract infections, hematuria, proteinuria, extrarenal cysts, cerebral aneurysms, cardiac valve involvement, renal calculi and gastrointestinal diverticuli [4–14]. Descriptions of the natural history of the disease are found in a large pre-dialysis era study [15, 16] and in several publications by Gabow and colleagues [17–20].

The gene presumed to be involved in the occurrence of the majority of cases of ADPKD (locus PKD1) was localized in 1985 to the short arm of chromosome 16 in families of northern European descent [21, 22]. Since then a number of papers and abstracts have appeared refining the genetic map of the region containing PKD1 and demonstrating that at least one other gene is associated with the presentation of this disease [23–30]. The genetic heterogeneity was first noted in two families of Italian origin [26, 27], suggesting a possible founder effect. Later a Danish family was noted to lack linkage to the PKD1 region [28] and two Newfoundland families gave data strongly suggestive of lack of linkage [29]. Some results have suggested that the unusual genetic form(s) of ADPKD might be associated with a less aggressive progression [28–30]. The locus name PKD3 has been reserved for this second type of ADPKD by the Human Gene Mapping Nomenclature Committee [41].

The experience of ADPKD in Toronto, Ontario is reviewed in this paper. Group 1 contained 19 families who have been studied with genetic markers to test for genetic heterogeneity of the disease in the Ontario population.

Group 2 included 80 ADPKD patients obtained from Toronto nephrologists, utilizing a structured questionnaire. Data from this group was studied for the incidence of non-renal complications and the mean age of onset of symptomatology.

Finally, group 3 comprised 4449 individuals who entered ESRF in the Toronto region between the years 1981 and 1992. Of these patients 320 reached ESRF because of ADPKD and 4129 due to other conditions. Comparisons were made between the two groups for many parameters including age of entry into dialysis, frequency of death, mean age at death for those who died, and cause of death for those who died.

Methods

Group 1 included 132 individuals from 19 families with ADPKD referred by two Toronto area nephrologists (JMR and MS). All participants gave informed consent. DNA from these individuals was studied with two DNA probes previously shown to flank the gene for the usual form of ADPKD (PKD1). The $_{p}$alpha3′HVR.64 probe, detecting a linked DNA marker in a chromosome location with markedly different sex-specific recombination rates, maps 8 map units distal to the PKD1 gene

Received for publication April 7, 1993
and in revised form July 6, 1993
Accepted for publication July 6, 1993

in males and 1 unit distal to the PKD1 gene in females. The $_{p}$alpha3'HVR.64 probe was supplied by Professor D.J. Weatherall (Oxford University, Oxford, UK) [21]. This probe was previously called 3'HVR since it originated from the 3' hypervariable region of the alpha 1 chain of the hemoglobin gene (HBA1). The probe 24-1 (D16S80), which detects a polymorphism 4 map units proximal to the PKD1 gene in males and 0.5 map units from this gene in females, was donated by Dr. M.H. Breuning (Rijksuniversiteit, Leiden, the Netherlands) [24]. A subset of group 1 was studied with an additional five probes purchased from Collaborative Research Incorporated (CRI, Bedford, Massachusetts, USA) [23]. The five probes were CRI-090 (locus D16S45), CRI-0129 (D16S56), CRI-0133 (D16S58), CRI-0136 (D16S60) and CRI-0327 (D16S63).

DNA was extracted from blood samples obtained from cooperating individuals and investigated for restriction fragment length polymorphisms (RFLPs) by standard methods of restriction enzyme digestion, separation of fragments by agarose gel electrophoresis, blotting unto nylon membranes, hybridization to the radioactively-labeled DNA probes and detection of the separated restriction fragments by autoradiography [30]. The pattern of inheritance of the restriction fragments in each family was defined by inspection. Where appropriate, standard methods of statistical linkage analysis were used. Linkage analysis methods included pairwise lod scores [31] using the computer program LIPED [32].

The probability that an individual at risk for ADPKD will be diagnosed as having ADPKD increases with the individual's age. Therefore a statistical correction for errors due to variation in age of onset of the ADPKD was incorporated into the analysis [33]. This straight line age of onset correction used the probabilities of at-risk individuals actually carrying the ADPKD gene calculated by Bear et al [34] for different age groups. These probabilities are: 0.34 for the age interval 15 to 20 years; 0.14 for the interval 20 to 30 years; and 0.05 for the interval 30 plus years. Penetrance (the probability that an individual who carries the disease gene will be diagnosed as being affected) was considered to increase linearly from a value of 0.05 at birth to 0.99 at 40 years of age or older. The gene frequency of ADPKD was assumed to be 0.008.

The lod score is a measure of the relative odds in favor of linkage versus no linkage at different arbitrarily-chosen recombination values (θ) between 0 and 50%. The absence of linkage is equivalent to a recombination value of 50%. The odds values are expressed logarithmically (to the base ten) and are therefore called lods, an abbreviation for the term "logarithm of the odds." The best estimate of the recombination frequency between two linked loci (maximum likelihood method) is taken to be the recombination value at which the lod score is maximal. Linkage is considered to be present when the lod score is $\geq +3$ (odds 1000:1 in favor of linkage) in cases where there is no prior reason to believe that linkage should be present. Linkage of an ADPKD locus to the studied chromosome 16 markers has been demonstrated previously in a large number of families [21–25]. Linkage is excluded when the lod score is ≤ -2, (odds in favor of linkage 1:100) and the data are inconclusive when the lod score is between -2 and $+3$.

To more efficiently use data from three or more loci, data were also analyzed by a multilocus linkage analysis method, the LINKMAP program of the LINKAGE package of programs [35, 36]. This method varies the position of one locus (here the ADPKD locus) over a fixed map of the linked markers to detect the most likely position of the variable marker. The age of onset was also corrected for LINKMAP, here as a step function, based on the different liability classes described previously by Bear et al [34].

Group 2 data were obtained from the outpatient charts of 80 patients diagnosed with ADPKD, obtained from about two thirds of Toronto nephrologists actively engaged in clinical practice. These nephrologists were selected solely by their agreement to participate in the study after telephone or letter contact by the investigating nephrologist (JMR). These nephrologists were associated with four of the major University of Toronto affiliated hospitals: Saint Michael's Hospital, Sunnybrook Hospital, the Toronto Hospital, or the Wellesley Hospital. Diagnostic testing was performed at all of these hospitals. One patient from group 1 was also contained in group 2. The charts were reviewed by a medical student (A.W.). Chart review was performed utilizing a simple, structured abstraction data collection instrument designed by A.W. and J.M.R. The instrument was a questionnaire containing queries formatted to be answered yes or no. The questions searched for information concerning hypertension, non-renal manifestations such as hepatic cysts, cardiac valve malformations, and disease symptomatology such as abdominal fullness or dysuria or increased urinary frequency. The presence or absence of flank pain was assessed.

Classification of a structure as a cyst was based on palpation at clinical examination or on a written radiologist's report. The radiological criterion for a cyst was that it showed through transmission of the ultrasonic beam on ultrasound. Cysts could be detected at less than one millimeter in size. In the ovary structures under 2.5 centimeters were not classified as cysts, unless more than two were present, to avoid confusion with ovarian follicles. Vaginal probes were not used for the ultrasound examination.

Radiological diagnosis of renal calculi was based on acoustic shadowing.

Signs and symptoms of cardiac valve involvement assessed included mitral valve prolapse murmur, chest pain, cardiac arrythmia, aortic insufficiency, aortic regurgitation murmur and/or echocardiogram.

Symptommatic intracranial aneurysm was defined as presentation with symptoms of subarachnoid hemorrhage followed by definitive investigation.

Diagnostic criteria for hypertension included blood pressure measurement of 140/90 on repeated measurements. Uncontrolled hypertension was defined as blood pressure in the hypertensive range on at least three separate occasions. Patients being maintained on antihypertensive medication were defined as hypertensive, regardless of present blood pressure value.

The data were stored and analyzed on an IBM compatible personal computer using the database software program DBase IV (BORLAND, Scotts Valley, California, USA). Simple mathematical means and percentages were calculated.

Data from patients in group 3 were collected by the Toronto Region Dialysis Registry, and included information on 4449 individuals who entered ESRF in the Toronto region between the years 1981 and 1992. Of these patients 320 had reached

ESRF because of ADPKD and 4129 due to other conditions. The Toronto Region Dialysis Registry was begun in 1981 to collect and to analyze information pertaining to the dialysis population of Metropolitan Toronto. Originally funded by the Kidney Foundation and industry, it is now part of the regional Multiple Organ Retrieval and Exchange (M.O.R.E.) Program. The database receives information from all chronic dialysis programs in the Greater Toronto (Central East Ontario) region. These include: Credit Valley Hospital, Hospital for Sick Children, Orillia Soldiers' Memorial Hospital, Oshawa General Hospital, Riverdale Chronic Care Hospital, Sheppard Centre Self Care Dialysis Unit, St. Joseph's Health Care Centre, St. Michael's Hospital, Sunnybrook Health Science Centre, The Toronto Hospital (General and Western Divisions), and The Wellesley Hospital.

The Toronto Region Dialysis Registry collects sociodemographic and medical data on all patients entering end-stage renal disease (ESRD) programs. Patients with acute renal failure are not included. An initial registration form is completed by the attending nephrologist or nurse for each new patient. The information requested includes primary renal disease diagnosis, renal biopsy results, if any, and risk factors present at the time renal replacement therapy is initiated. The risk factors section requires an indication of whether or not other medical conditions which may adversely affect the patients' prognosis are present (yes or no). Such conditions include coronary artery disease, a history of cigarette smoking, pulmonary edema, congestive heart failure, diabetes mellitus, cerebro-vascular accident, peripheral vascular disease, malignancy, chronic obstructive lung disease, hypertension, and any other serious illness (specified) that would shorten life expectancy to less than five years.

Regular follow-up demographics are completed by nephrology nurses in each dialysis program, providing up-to-date information on new patients, changes in treatment, transfers between programs, deaths, transplants, and allograft failure. Primary cause of death is reported using codes based on the coding system of the Canadian Organ Replacement Registry. Specific causes of death are categorized as cardiac, vascular, infection, liver disease, gastrointestinal, treatment stopped, other specified causes, and undetermined. Cardiac causes of death, for example, include: myocardial ischemia and infarction, cardiac arrest due to hyperkalemia, hemorrhagic pericarditis, cardiac arrest due to hypokalemia, cardiac arrest due to fluid overload, cardiac arrest—cause unknown, hypertensive cardiac failure, other causes of cardiac failure. Cerebro-vascular accident (CVA), which is included in the vascular category, is reported separately in this paper because of the incidence of death from CVA among ADPKD patients.

Twenty-two of the 80 patients in group 2 had reached ESRF, and are included in group 3. These have been analyzed separately from the entire group 3 block for issues addressed in both groups 2 and 3 to see if they agree with group 3 as a whole. Nine individuals from eight families in group 1 were also included in group 3.

Data were analyzed by inspection, and the relevance of any apparent differences between groups was assessed by the Student's t-test or a χ^2 comparison analysis [37]. A life table survival analysis procedure (the LIFEREG procedure) was performed to analyze lengths of survival after ESRF between ADPKD and non-ADPKD patients [37].

Table 1. Summary of DNA restriction fragment length polymorphism (RFLP) studies on ADPKD families using the DNA probe $_p$alpha 3'HVR

	Families	Individuals
Structure incomplete or inappropriate	4	6
Sporadic case	2	6
DNA uninformative	1	11
Informative	12	109
Total	19	132

Results

Table 1 illustrates the results of genetic analysis of 19 ADPKD families (132 individuals; group 1) with chromosome 16 linked probes. As expected because of its large number of possible polymorphic fragments, the most informative marker in our families was $_p$alpha3'HVR.64. Twelve of the 19 families (63%), comprising 109 individuals, were fully informative for genetic analysis using $_p$alpha3'HVR.64. Seven families (37%) were not informative for the following reasons: (a) linkage phase could not be assigned in six families (32%) either because of incomplete or inappropriate family structure (4 of the 6 families; 21.1%), the occurrence of the ADPKD in one individual only (sporadic case; 2 of the 6 families; 10.5%); and (b) in one family (5.3%) the DNA marker was uninformative, that is, the patient was homozygous for the marker. Of the twelve families informative for linkage, ten (83%) showed results compatible with linkage of ADPKD to the DNA markers.

One family gave results suggesting that the ADPKD segregating in its members was not linked to the chromosome 16 probes used. This family was studied extensively with all seven RFLP probes, three of which were sufficiently informative for statistical linkage analysis. Pairwise lod scores between $_p$alpha3'HVR.64 and ADPKD and between CRI-090 and ADPKD excluded linkage in this family at recombination fractions of up to 0.06 and 0.05, respectively. The lod score was inconclusive for linkage between CRI-0136 and the ADPKD locus. Multipoint linkage analysis by LINKMAP excluded the ADPKD locus from 0.20 morgans from the distal side of $_p$alpha3'HVR.64 to 0.43 morgans on the proximal side when $_p$alpha3'HVR.64 was arbitrarily set at 0.00. This is the genetic interval containing the PKD1 locus. These results were supported when the data were analyzed using only affected family members (to reduce the risk of error due to misclassification of affected members as unaffected because they were too young to manifest the disease). In this case even with the reduced numbers of family members analyzed, the lod equivalent at -2.32 with $\theta = 0$ between ADPKD and $_p$alpha3'HVR.64 excluded linkage. The lod equivalent between CRI-090 and ADPKD was -1.67 and between CRI-0136 and ADPKD was -1.78, strong evidence against linkage in both cases. The lod equivalent never rose above -1.58 over the whole region analyzed using affected family members only, strongly suggesting no linkage with the ADPKD locus over this PKD1 containing region. This family has been reported elsewhere in greater detail [30].

Table 2. Comparison of the frequency of systems involvement in ADPKD between a literature summary [19] and the Toronto study

System	Literature	Toronto study
Genitourinary		
Kidney	100%	99%
Ovary	Unknown	13%
Gastrointestinal		
Hepatic	40–60%	46%
Pancreatic	Rare	0%
Diverticulae	83%	4%
Cardiovascular		
Valvular	30% (Echo)	5%
Intracranial aneurysm	0–40% (10%)	1.25%

Data are expressed as percent of patients studied. The probe was $_{p}$alpha 3'HVR.

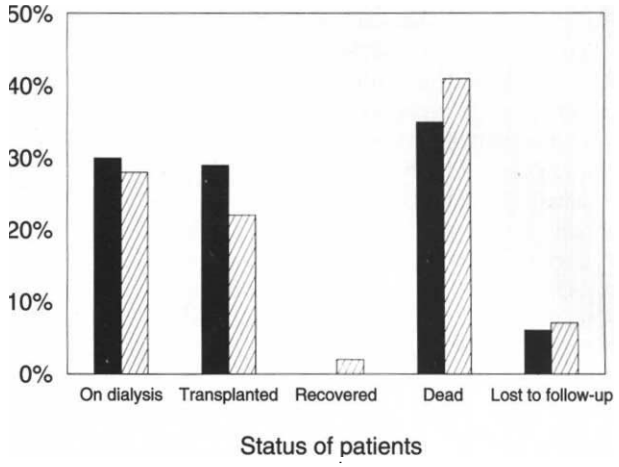

Fig. 1. *Status of Toronto Area ADPKD (■) and non-ADPKD (▨) patients with end-stage renal disease, obtained from the Toronto Region Dialysis Registry expressed as percent of total patients in the group.*

The results from one final family suggested an absence of linkage to the genetic markers, but this latter family could not be studied further. The presence of these two families in our population suggests that the frequency of an additional gene or genes for ADPKD is from 8 to 17% in our population.

The frequency of sporadic or non-familial cases, possibly resulting from new mutation, in our population was 2 of 19 or 10%. All surviving family members of one of these individuals, including his parents, sibling, and his grandmother had negative abdominal ultrasound examinations. Formal paternity testing for this case was not performed, but the RFLP results from probe $_{p}$alpha3'HVR.64 were in agreement with paternity as stated by the family. Interestingly, this patient also was diagnosed to have an adult form of cystic fibrosis for which there was again no family history.

Analysis of charts from group 2, which included mainly pre-ESRF (predialysis) patients (58 of 80 or 72.5%) to determine the frequency of systems involved in ADPKD showed kidney involvement in 99% of cases (Table 2) (The single exception was a brother of an individual with extensive kidney and liver cysts who himself had multiple liver cysts but no discernable kidney involvement). Thirteen percent of females (3 of 23) examined by ultrasound (US) or by US and computed tomography (CT) had ovarian cysts detected. Thirteen of the women studied were 50 years of age or greater at time of CT (postmenopausal) and none of these patients had cysts. Timing of the study in relationship to the woman's menstrual cycle and hormone replacement status in the postmenopausal women was not known.

Involvement of the gastrointestinal system was frequent. Forty-six percent (32 of 67) of patients examined by US or by US and CT, had hepatic cysts, some with severe involvement. One patient examined by CT only, had a negative result. Thirty-two patients examined by US were stated to have no liver cysts. Four patients with no liver cysts had no US or CT. When males and females were analyzed separately, only 41.3% (19 of 46) of males had hepatic cysts compared to 56.5% (13 of 23) of females $\chi^2 = 1.4$; $P = 0.23$; NS). The mean age of all 32 patients (males and females) with hepatic cysts was 38.8 ± 12.3 years in Toronto versus 42.3 ± 2.0 years in a recently published series [19]. The mean age of those without cysts was 36.3 ± 15.9 years in Toronto against 32.5 ± 1.4 years in the study by Gabow and Schrier [19]. The mean age of females with cysts was slightly younger (37.8 ± 11.4 years) compared to males (39.4 ± 13.2 years; NS). The overall male/female ratio in the present group was 1.5 or 19 males versus 13 females. The mean age of females with cysts was higher than that of females without hepatic cysts (37.8 ± 11.4 vs. 28.5 ± 14.9 years; NS). No pancreatic cysts were noted in group 2 patients. Symptomatic intestinal diverticulae were noted in 4% of group 2 patients.

Renal calculi were recorded in 8 of 80 (10%) of patients. Five percent of ADPKD patients had clinically apparent cardiac valve involvement.

Symptomatic intracranial aneurysm occurred in 1.25% of these patients.

Chart inspection demonstrated that most asymptomatic patients were not screened either by recorded systems review or by formal objective testing for intracranial aneurysm, cardiac valvular lesions or intestinal diverticulae. In fact, the only clinical test used in the majority 67 of 80 (84%) of patients was abdominal ultrasound. This examination gave objective data on the presence or absence of cyst occurrence in different organs.

Demographic data were analyzed for group 3. The status of the two types of ESRF patients (ADPKD and non-ADPKD patients) is shown in Figure 1. Equivalent proportions of patients in each group remained on dialysis or died. However, about 29% of ADPKD patients have received a functioning transplant versus 21% of non-ADPKD patients ($\chi^2 = 8.582$; $P = 0.003$). Two percent of non-ADPKD patients have recovered renal function and, not surprisingly, none of the ADPKD patients have done so. Six to seven percent of patients were lost to follow-up in both groups.

The mean age at entry into ESRF for the 320 patients with ADPKD was older (54.4 ± 10.9 years) than for the 4,129 non-ADPKD patients (50.4 ± 19.4 years; $P = 0.0001$ by t-test; Fig. 2). The mean age at entry into ESRF for patients with ADPKD of the type not linked to the chromosome 16 probes (PKD3) was much higher: 69.5 years (a difference of +15.2 years). This average age, however, was derived from only two patients. Mean age of entry into ESRF did not differ with or without hypertension. Sixty-four percent (205) of the 320 ADPKD patients with ESRF suffered from hypertension and

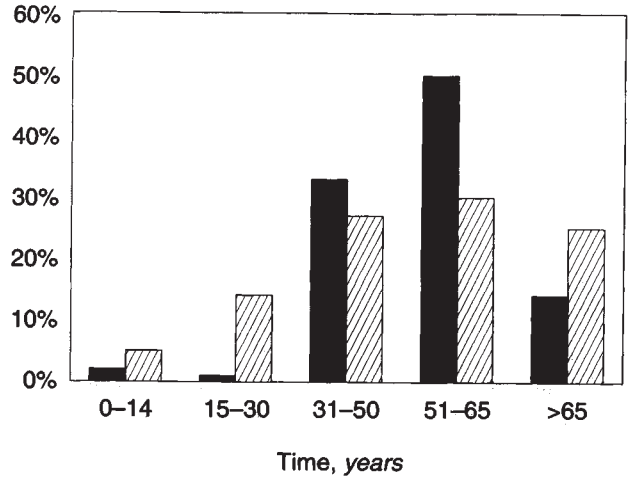

Fig. 2. *Age at entry to end-stage renal failure in years for ADPKD (■) and non-ADKPD (▨) patients, obtained from the Toronto Region Dialysis Registry.*

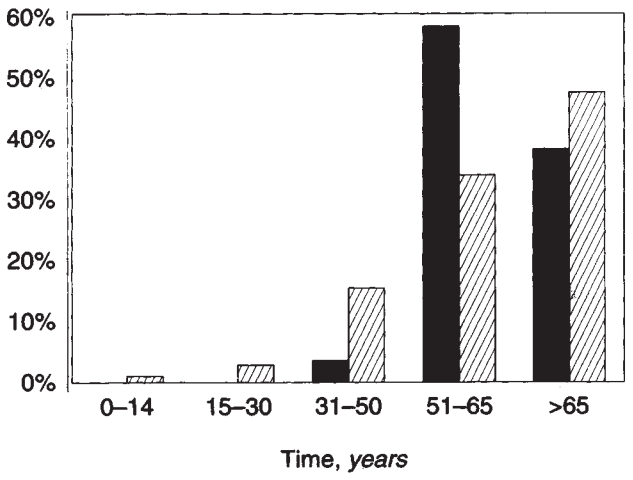

Fig. 3. *Age at death for ESRF patients who died, obtained from the Toronto Region Dialysis Registry.* Symbols are: (■) ADPKD patients; (▨), non-ADPKD patients.

entered ESRF at a mean age of 54.9 ± 11.0 years. Thirty-six percent had no hypertension and entered ESRF at mean age 53.5 ± 10.5 years).

Thirty-five percent (113) of the ADPKD patients died during the reporting period versus 38.4% (1708) of the non-ADPKD patients (Fig. 3). The average age at death was 63.9 ± 8.5 years for ADPKD versus 62.1 ± 14.8 years for the 1,708 non-ADPKD patients (P = 0.05). When the one ESRF patient whose ADPKD was known to be of the PKD3 type was dropped from the analysis, the average age of death remained unchanged at 63.9 ± 8.5 years. None of six other ESRF patients whose families were studied with DNA probes (in group 1) and whose disease was apparently linked with the chromosome 16 probes died. Their average age at time of study was 59.8 years. An additional individual from group 1 had ESRF. This family's results suggested PKD3 type ADPKD but could not be further studied. This person was 56 years old. Years of survival after ESRF measured by the LIFEREG procedure was significantly less for non-ADPKD than ADPKD patients (χ^2 = 7.794; P = 0.005; Fig. 4A). The significance of this difference was lost when patients suffering from diabetes were dropped from the analysis (χ^2 = 1.166; P = 0.28), although the ADPKD patients still appeared to show a longer survival than the non-ADPKD patients (Fig. 4B). The leading cause of death in both groups was cardiac (34% in ADPKD, 42% in non-ADPKD; χ^2= 2.68; P = 0.10), however, a significantly increased incidence of death from CVA (11%) in ADPKD versus non-ADPKD (6%; χ^2 = 4.450; P = 0.04) and infection (20.4% ADPKD vs. 12.5% non-ADPKD; χ^2 = 5.839; P = 0.02) was observed (Table 3).

Only four of twelve ADPKD patients (33%) who died of CVA also suffered from hypertension compared to 69 of 98 non-ADPKD patients (70.4%), suggesting that a significant number (up to 66%) of ADPKD patients who died of CVA did not die of "stroke" secondary to hypertension. The age at death of ADPKD patients with CVA and hypertension was 60.7 ± 5.8 years, significantly younger than the age of non-ADPKD patients with CVA and hypertension (64.3 ± 11.4 years (χ^2 = 6.583, P = 0.01). The remaining CVA patients in the ADPKD group were eight persons (66%) without hypertension who died at a mean age of 66.6 ± 9.3 years. In the non-ADPKD group 29 individuals (29.6%) were without hypertension and died at a mean age of 59.9 years.

Table 4 classifies the deaths due to infection by infectious subtype. No one particular type of infection explained the increase of death due to infection. Rather, each subclass of bacterial infection showed a slight increase in the ADPKD patient population.

Discussion

The incidence of Ontario ADPKD patients whose disease shows genetic linkage to the chromosome 16, by short arm probes which have been previously linked to ADPKD in Europe, is at least 83%. In at least 8% and possibly up to 17% of Ontario families with ADPKD, the disease is not linked to the previously reported probes (PKD3). One of the families, in whom genetic linkage to chromosome 16 markers did not occur, was studied extensively to prove the absence of genetic linkage and has been reported elsewhere [30]. This finding confirms the discovery of genetic heterogeneity published in previous reports [26–30], demonstrates its presence in an additional population group, and assists in refining a frequency estimate for the alternate (PKD3) gene(s).

Age at entry to ESRF has changed since 1957 for ADPKD patients. In Dalgaard's 1957 study [15, 16] the average age at death was 51.5 years, and death was said to occur about three years after onset of uremia, putting onset of uremia at an average age of 48.5 years. The mean age at onset of ESRF in 1982 to 1992 was 54.4 ± 10.9 years for ADPKD patients. Therefore it is fair to conclude that patients from 1981 to 1992 may lose their renal function about six to seven years later compared to those in 1957. This improvement may result from better hypertension control and/or better control of infection. In addition, the geographic isolation from Dalgaard's (Danish) group may influence the difference in age of onset of ESRF in the present study group, either having allowed the accumulation of different intragenic or extragenic mutations influencing ADPKD in the present population, or allowing interaction of different environmental variables with the original ADPKD

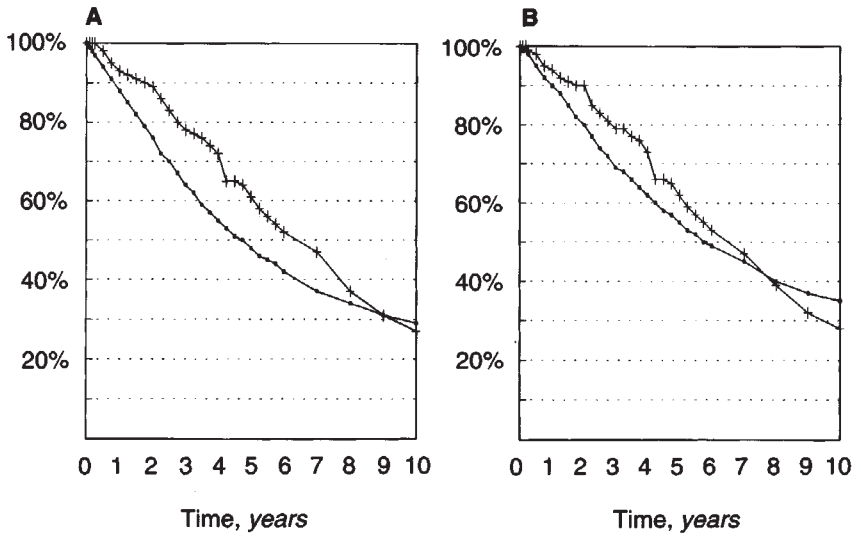

Fig. 4. *Survival curves for ADPKD (+) and non-ADKPD (⊟) patients after ESRF graphed as percent survival versus years after ESRF, generated by life table analysis from the Toronto Region Dialysis Registry.* **(A)** Data including all patients in both groups. **(B).** Data excluding patients with diabetes from both groups.

Table 3. Comparison of causes of death between patients who had ADPKD and diseases other than ADPKD (Non-ADPKD) from 1981–1992[a]

Cause of death	ADPKD	Non-ADPKD
Cardiac	34%	42%
Vascular	1%	3%
CVA	11%[b]	6%[b]
Infection	20%[b]	12%[b]
Gastrointestinal	4%	2%
Liver disease	0%	<1%
Other causes	12%	14%
Undetermined	10%	10%
Treatment stopped	10%	12%

[a] Data obtained from the Toronto Region Dialysis Registry and expressed as percent of total deaths in each group (ADPKD = 113; Non-ADPKD = 1708)

[b] Significant differences between ADPKD and Non-ADPKD when analyzed by χ^2

Table 4. Comparison of specific infections causing death between patients who had ADPKD and diseases other than ADPKD (Non-ADPKD) from 1981–1992

Type of Infection	ADPKD	Non-ADPKD
Peritonitis	2.7%	1.5%
Septicemia	12.4%	8.3%
Bacterial pulmonary	1.8%	1.2%
Viral pulmonary	0.0%	0.4%
Fungal pulmonary	0.9%	0.2%
Tuberculosis	0.0%	0.1%
Generalized viral	1.8%	0.3%
Other infections	0.9%	0.5%

Data are expressed as the percent of total deaths in each group (ADPKD = 113; Non-ADPKD = 1708).

mutation(s) in the present population. Actual age of death in the ADPKD population, with all treatment improvements, including dialysis, is at a mean of 63.9 years or more than a decade (12.4 years) later than in 1957.

Of 320 patients with ADPKD, 205 had hypertension at the beginning of treatment for ESRF (64.1%). There was no difference in age at entry to ESRF or in age at death from all causes in patients with or without hypertension.

The incidence of hepatic cyst involvement is similar to that of previous series [19]. As noted in other studies, females seem to be more at risk for hepatic involvement and the frequency of hepatic cyst involvement tends to increase with age.

The frequency of involvement of other organ systems (such as cardiovascular and gastrointestinal) was much lower than that reported at other centers [17–19]. However, specific sensitive screening tests were used in the other centres to assess the presence of such involvement. The patients reported here were assessed symptomatically only. We infer therefore that the incidence of other organ involvement is underdiagnosed without deliberate screening.

Eleven percent of patients with ADPKD died of cerebrovascular accident (CVA). This was a five percent greater incidence than that in non-ADPKD patients. It is known that patients with ADPKD have an increased incidence of intracranial aneurysm and this extra five percent dying of CVA may represent ruptured intracranial aneurysms. This possibility is substantiated by the fact that only 1/3 of those dying of CVA in the ADPKD group suffered from hypertension. In addition, age at death of those dying of CVA with hypertension in the ADPKD group was significantly lower than that of those dying of CVA with hypertension in the non-ADPKD group. Previous work with decision analysis has suggested that the general medical risks of diagnostic cerebral angiography have outweighed its diagnostic benefits [38] for ADPKD patients. New information suggests that patients with ADPKD may have an even higher risk of such medical complications than the general population [11]. The development of the non-invasive techniques of high resolution computed tomography and magnetic resonance imaging [8, 11] allows diagnosis of aneurysms above 6 mm in size, which are more likely to rupture [39, 40]. We believe that all patients with ADPKD should be screened with high resolution computed tomography and/or magnetic resonance imaging in an effort to diagnose aneurysms at an earlier, treatable stage [8]. Since the deaths due to CVA in the ADPKD group occurred at an average age of 60.7 ± 5.8 years in the hypertension group

and 66.6 ± 9.3 years in the non-hypertension group, we believe that this screening of ADPKD patients should continue well into the seventh decade. We believe that the greatest "at risk" period for aneurysm rupture is in the 55 to 65 year age interval in the presence of hypertension, and possibly somewhat later in individuals who do not suffer from hypertension. The 11% incidence of death due to CVA has not changed dramatically since the predialysis era reports [14, 15] which noted 13% of deaths caused by CVA, 59% due to uremia, 6% to cardiac and 22% from other causes including infection. A high incidence of death due to infection still persists in ADPKD patients (20.4% vs. 12.5% in non-ADPKD ESRF patients). The increase of infectious deaths in ADPKD versus non-ADPKD patients is not solely a result of peritonitis or of graft infections but is actually a result of a general increase in all types of infections reported for the ESRF group. A review of the literature on infection in the ADPKD patients reveals case reports of single rare atypical infections in ADPKD patients [11–13]. These interesting observations suggest that the spectrum of involvement of ADPKD organ systems may also include an immunodeficiency defect. This possibility will be investigated in future studies.

In summary, ADPKD is a significant cause of renal failure in the Toronto population. Most of these families with ADPKD appear to have a disease linked to genetic markers on the short arm of chromosome 16 (PKD1). These markers could therefore be used for preclinical diagnosis of the condition in those families which are linked or in screening prospective, related organ donors in individual families. A number of complications can arise in patients with ADPKD including hepatic cysts, CVA and infections. The age of entry to ESRF and the age of death appears to have been delayed by over twelve years with modern methods of treatment.

Acknowledgments

The authors acknowledge the essential support of The Wellesley Hospital Renal Research Fund and of J.W.M. and W.G. Brissenden. We thank Dr. Andrew Pakstis from the laboratory of Dr. Ken Kidd for his generous support both technical and intellectual in the establishment of the linkage analysis programs in our laboratory. We also thank Drs. Pakstis and Kidd for helpful discussion and for performing critical data analyses on their VAX which were beyond the capacity of our computer.

Reprint requests to Janet M. Roscoe, M.D., Suite 310, Elsie K. Jones Building, 160 Wellesley Street East, Toronto, Ontario M4Y 1J3, Canada.

References

1. Scientific Advisory Board of the National Kidney Foundation Workshop, September 16, 1988. *Am J Kid Dis* 8:85–87, 1989
2. IGLESIAS CG, TORRES VE, OFFORD KP, et al: Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota. *Am J Kid Dis* 2:630–639, 1983
3. HODGKINSON KA, KERZIN-STORRAR L, WATTERS EA, HARRIS R: Adult polycystic kidney disease: Knowledge, experience, and attitudes to prenatal diagnosis. *J Med Genet* 27:552–558, 1990
4. DELANEY VB, ALDER S, BURNS FJ, LICINIA M, SEGEL DP, FRALEY DS: Autosomal dominant polycystic kidney disease: Presentation, complication, and prognosis. *Am J Kid Dis* 5:104–111, 1985
5. WAKABAYASHI T, FUJITA S, OHBORA Y, SUYAMA T, TAMAKI N, MATSUMOTO S: Polycystic kidney disease and intracranial aneurysms. *J Neurosurg* 58:488–491, 1983
6. RYU S-J: Intracranial hemorrhage in patients with polycystic kidney disease. *Stroke* 21:291–294, 1990
7. CHAUVEAU D, SIRIEIX M-E, SCHILLINGER F, LEGENDRE C, GRÜNFELD J-P: Recurrent rupture of intracranial aneurysms in autosomal dominant polycystic kidney disease. *Br Med J* 301:966–967, 1990
8. TORRES VE, WIEBERS DO, FORBES GS: Cranial computed tomography and magnetic resonance imaging in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1:84-90, 1990
9. FEHLINGS MG, GENTILI F: The association between polycystic kidney disease and cerebral aneurysms. *Can J Neurol Sci* 18:505–509, 1991
10. LOZANO AM, LEBLANC R: Cerebral aneurysms and polycystic kidney disease: A critical review. *Can J Neurol Sci* 19:222–227, 1992
11. CHAPMAN AB, RUBINSTEIN D, HUGHES R, STEARS JC, EARNEST MP, JOHNSON AM, GABOW PA, KAEHNY WD: Intracranial aneurysms in autosomal dominant polycystic kidney disease. *N Engl J Med* 327:917–920, 1992
12. SEKIMOTO M, HAYASAKA S, SETOGAWA T, SHIGENO K: Endogenous *Escherichia coli* endophthalmitis in a patient with autosomal-dominant polycystic kidney disease. *Ann Ophthalmol* 23:458–459, 1991
13. RIEDASCH G, MOHRING K, BIHL H: Septische Komplikationen bei polyzystischer nierendegeneration. *Helv chir acta* 53:265–268, 1986
14. BRETAN PN, PRICE DC, MCCLURE RD: Localization of abcess in adult polycystic kidney by indium-111 leukocyte scan. *Urology* XXXII(2):169–171, 1988
15. DALGAARD OZ: Bilateral polycystic disease of the kidneys. *Acta Med Scand* 156 (Suppl. 328):1–25, 1957
16. DALGAARD OZ: Polycystic disease of the kidneys, in *Disease of the Kidneys*, edited by MB STRAUSS, LG WELT, Boston, Little, Brown & Co., 1963, pp 1223–1258
17. GABOW PA: Autosomal dominant polycystic kidney disease—More than a renal disease. *Am J Kid Dis* XVI(5):403–413, 1990
18. GABOW PA: Polycystic kidney disease: Clues to pathogenesis. *Kidney Int* 40:989–996, 1991
19. GABOW PA, SCHRIER RW: Pathophysiology of adult polycystic kidney disease. *Adv Nephrol* 18:19–32, 1989
20. GABOW PA, INKLERMAN DW, HOLMES JH: Polycystic kidney disease: Prospective analysis of nonazotemic patients and family members. *Ann Intern Med* 101:238–247, 1984
21. REEDERS ST, BREUNING MH, DAVIES KE, NICHOLLS RD, JARMAN AP, HIGGS DR, PEARSON PL, WEATHERALL DJ: A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. *Nature (Lond)* 317:542–544, 1985
22. REEDERS ST, BREUNING MH, CORNEY G, JEREMIAH SJ, MEERA KHAN P, DAVIES KE, HOPKINSON DA, PEARSON PL, WEATHERALL DJ: Two genetic markers closely linked to adult polycystic kidney disease on chromosome 16. *Br Med J* 292:851–853, 1986
23. REEDERS ST, KEITH T, GREEN P, GERMINO GG, BARTON NJ, LEHMANN OJ, BROWN VA, PHIPPS P, MORGAN J, BEAR JC, PARFREY P: Regional localization of the autosomal dominant polycystic kidney disease locus. *Genomics* 3:150–155, 1988
24. BREUNING MH, SNIJDEWINT FGM, BRUNNER H, VERWEST A, IJDO JW, SARIS JJ, DAUWERSE JG, BLONDEN L, KEITH T, CALLEN DF, HYLAND VJ, XIAO GH, SCHERER G, HIGGS DR, HARRIS P, BACHNER L, REEDERS ST, GERMINO G, PEARSON PL, VAN OMMEN GJB: Map of 16 polymorphic loci on the short arm of chromosome 16 close to the polycystic kidney disease gene (PKD1.) *J Med Genet* 27:603–613, 1990
25. SOMLO S, GERMINO GG, WIRTH B, WEINSTAT-SASLOW D, BARTON N, GILLESPIE GAJ, FRISCHAUF AM, REEDERS ST: The molecular genetics of autosomal-dominant polycystic kidney disease of the PKD1 Type, in *Polycystic Kidney Disease. Contrib Nephrol* (vol 97), edited by MH BREUNING, M DEVOTO, G ROMEO, Basel, Karger, 1992, pp 101–109
26. KIMBERLING WJ, FAIN PR, KENYON JB, GOLDGAR D, SUJANSKY E, GABOW PA: Linkage heterogeneity of autosomal dominant polycystic kidney disease. *N Engl J Med* 319:913–918, 1988
27. ROMEO G, DEVOTO M, COSTA G, RONCUZZI L, CATIZONE L, ZUCCHELLI P, GERMINO GG, KEITH T, WEATHERALL DJ, REEDERS ST: A second genetic locus for autosomal dominant polycystic kidney disease. *Lancet* 2:8–11, 1988

28. NØRBY S, SØRENSEN AWS, BOESEN P: Non-allelic genetic heterogeneity of autosomal dominant polycystic kidney disease? in *Genetics of Kidney Disorders,* edited by C BARTSOCES, *Proceedings of Fifth International Clinical Genetics Seminar,* New York: Alan R. Liss, 1989, pp 83–88
29. PARFREY PS, BEAR JC, MORGAN J, CRAMER BC: The diagnosis and prognosis of autosomal dominant polycystic kidney disease. *N Engl J Med* 323:1085–1090, 1990
30. BRISSENDEN JE, ROSCOE JM, SIMPSON NE, SILVERMAN M: Linkage exclusion between the autosomal dominant polycystic kidney disease locus and chromosome 16 markers in a new family. *J Am Soc Nephrol* 2:913–919, 1991
31. MORTON NE: Sequential tests for linkage. *Am J Hum Genet* 7:277–317, 1955
32. OTT J: Estimation of the recombination fraction in human pedigrees. Efficient computation of the likelihood for human linkage studies. *Am J Hum Genet* 26:588–597, 1974
33. HODGE SE, MORTON LA, TIDEMAN S, KIDD KK, SPENCE MA: Age of onset correction available for linkage analysis (LIPED) [News and Comments]. *Am J Hum Genet* 31:761–762, 1979
34. BEAR JC, MCMANAMON P, MORGAN J, PAYNE RH, LEWIS H, GAULT MH, CHURCHILL DN: Age at clinical onset and at ultrasonographic detection of adult polycystic kidney disease: Data for genetic counselling. *Am J Med Genet* 18:45–53, 1984
35. LATHROP GM, LALOUEL J-M, JULIER C, OTT J: Strategies for multilocus linkage analysis in humans. *Proc Natl Acad Sci USA* 81:3443–3446, 1984
36. LATHROP GM, LALOUEL JM, JULIER C, OTT J: Multilocus linkage analysis in humans: Detection of linkage and estimation of recombination. *Am J Hum Genet* 37:482–498, 1985
37. *SAS Institute Inc. SAS/STAT™ User's Guide.* Release 6.03 Edition, Cary, SAS Institute Inc., (chapt 8) Introduction to Survival Analysis Procedure, pp 87–88; (chapt 21) The LIFEREG Procedure, pp 641–666; (chapt 19), The FREQ Procedure, pp 519–548; (chapt 33) The TTEST Procedure, pp 941–947; 1988
38. DE LA MONTE SM, MOORE GW, MONK MA, HUTCHINS GM: Risk factors for the development and rupture of intracranial berry aneurysms. *Am J Med* 78:957–964, 1985
39. WIEBERS DO, WHISNANT JP, SUNDT TM JR, O'FALLON M: The significance of unruptured intranial saccular aneurysms. *J Neurosurg* 66:23–29, 1987
40. LEVEY AS, PAUKER SG, KASSIRER JP: Occult intracranial aneurysms in polycystic kidney disease: When is cerebral angiography indicated? *N Engl J Med* 308:986–994, 1983
41. MCALPINE PJ, SHOWS TB, BOUCHEIX C, HUEBNER M, ANDERSON WA: The 1991 catalog of mapped genes and report of the nomenclature committee. *Cytogenet Cell Gen* 58:5–102, 1991