

*Original Article***Frequency and impact of autosomal dominant polycystic kidney disease in the Seychelles (Indian Ocean)**C. Yersin¹, P. Bovet^{2,3}, J.-P. Wauters⁴, D. F. Schorderet⁵, G. Pescia⁵ and F. Paccaud³

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Abstract

Background. As little such data is available in African populations, we investigated the prevalence of ADPKD and the impact of the disease in the Seychelles islands, where approximately 65% of the population is of African descent and 30% of Caucasian or mixed descent.

Methods. Prevalent cases were identified over a 3-year period by requesting all the doctors in the country (most of them are employed within a national health system) to refer all presumed or confirmed cases and by systematically examining the family members of all confirmed cases. The diagnosis was based on standard criteria including ultrasonographic findings and family history.

Results. Forty-two cases were identified in this population of 74 331 inhabitants, a total prevalence (per 100 000 total population) of 57 (95% CI, 41–76). All but one of the cases were of Caucasian descent so that the prevalence rates of the disease in the populations of Black and Caucasian descents were respectively 2 (0–11) and 184 (132–249). The prevalence rates of the gene(s) carriers were estimated to be 75 (45–117) in the total population respectively 6 (0–33) and 236 (140–372) in the Black and Caucasian populations. Haplotype analysis in 58 cases from three families showed a common DNA fragment in all affected individuals. Cases had significantly higher blood pressure compared to the general population and 21% had serum creatinine higher than 120 $\mu\text{mol/l}$. Among the established pedigrees, mean age of death between 1960 and 1995 (haemodialysis was introduced in 1992) was younger in subjects with than those without ADPKD (50.5 vs 67.7 years; $P < 0.001$).

Conclusions. In the Seychelles, ADPKD clusters in the Caucasian population (possibly a founder effect), is rare in individuals of black descent, and is associated with substantial clinical and survival impact.

Key words: Africa; autosomal dominant polycystic kidney disease; developing countries; DNA analysis; epidemiology; hypertension; renal failure

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) affects about 1 in 1000 persons in Caucasian populations [1] and may be 2.5–15 times more frequent than other common hereditary disorders such as cystic fibrosis and sickle-cell disease [2]. Two genes responsible for the disease have been identified and there is some evidence for the existence of a third locus [3]. Spontaneous mutations arise rarely and account for less than 10% of all cases [2]. Since the disease is transmitted in an autosomal dominant mode, every offspring of an affected parent has a 50% risk of inheriting and developing the disease [1]. The phenotypic presentation is expressed generally years later [3]. The disease is characterized by cyst formation in ductal organs particularly the kidney and the liver and by gastrointestinal, cardiovascular and other abnormalities [3–5]. ADPKD frequently results in hypertension and renal failure, and death often relates to cardiac and cerebrovascular complications [6,7].

ADPKD epidemiology was rarely studied in non-Caucasian populations and the impact on health of this chronic disease has not yet been assessed in developing countries. We therefore conducted a population-based study to determine the prevalence of ADPKD and the frequency of hypertension and renal failure associated with the disease in the Seychelles, the population of which is of predominantly black African descent. Survival was compared in individuals with and without ADPKD to evaluate the prognosis of this chronic disease in a developing country with limited resources for case management.

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Subjects and methods

The study area covered the whole territory of the Seychelles (445 km²). The first inhabitants settled in Seychelles in the 1770s and were of French and African origin. The population has grown to 74 331 people in 1994 [8]. The ethnic distribution of the population is now considered to be African in 65%, European (Caucasian) in 10%, Asiatic in 5%, and mixed in 20% [9]. The national gross domestic product per capita has grown from US\$ 800 to US\$ 6000 between 1976 and 1995 [10], and Seychelles is now considered as a middle level income country.

Two strategies were used to identify all prevalent cases in the entire population. First, all physicians, surgeons, paediatricians, radiologists, and pathologists of the country (around 100 doctors, most of them employed within a national health system) were repeatedly informed of the study and requested to refer to one of us all patients with presumed or confirmed 'polycystic kidney disease'. Noticeably, medical care is equally and easily accessible to all inhabitants as it is delivered free of charge through as many as 21 clinics and hospitals evenly spread throughout the country. In addition, more than 25% of all deaths undergo post-mortem examination, which further curtails the chance that affected families go undetected. Secondly, the family members of the confirmed cases were investigated to identify other ADPKD cases and pedigrees were established for all families with ADPKD cases. Diagnostic investigations were declined by 35 out of 118 at-risk subjects of the established pedigrees. The study period spanned from January 1993 to December 1995. All examined subjects gave informed consent to participate in the study, which was approved by the Ministry of Health of Seychelles.

The diagnosis of ADPKD used in this study followed standard criteria based on ultrasonographic or post-mortem findings and a family history of polycystic kidney disease [11]. Ultrasound scans were performed by the same radiologist. We used ultrasonographic criteria established by Ravine for the diagnosis of ADPKD 1 (the PKD1 locus generally accounts for more than 85% of ADPKD families [3]), i.e. the presence of at least two renal cysts (unilateral or bilateral) in individuals at risk aged less than 30 years; the presence of at least two cysts in each kidney in patients aged 30–59 years; and the presence of at least four cysts in each kidney in patients aged 60 years and above [12]. If there was no positive family history of cystic renal disease, the subject was considered to have ADPKD on the basis of typical ultrasonographic findings. These cases, referred to in this study as 'isolated cases', are probably the result of new mutations although an unacknowledged father with ADPKD may not be ruled out. In this paper, subjects with definite kidney ultrasonographic findings are considered to have 'clinically expressed ADPKD'. A subject was considered to be at risk for carrying a gene for ADPKD if he was living in Seychelles during the study period and had an affected parent, sibling, or child.

Haplotype analysis was performed on blood samples obtained from 58 individuals belonging to three unconnected families. DNA was extracted from peripheral leukocytes according to a standard protocol. Haplotype analysis was performed with SM7 and KG8, two microsatellite markers linked to the disease [13,14]. SM7 is located about 400 kb telomeric of PKD1 while KG8 lies in its 3' untranslated region. PCR assays were carried out in a total volume of 10 µl using a Perkin-Elmer Cetus 9600 machine. The reaction mixes and PCR conditions were those described for the

specific primers. Radioactive PCR products were resolved on denaturing polyacrylamide gels and detected by autoradiography.

Blood pressure and serum creatinine were measured in all cases. Blood pressure in subjects with ADPKD was compared with values in the general population. Blood pressure in the general population came from a population-based survey of cardiovascular risk factors carried out in 1989 using a random sample of 1081 adults [15]. The average of the four measurements made of duplicate blood pressure readings at the time of two visits was considered in ADPKD subjects while the average of the last two of three readings at the time of one single visit was considered in the participants to the survey. As creatinine clearance was not available for several patients, renal failure was defined if serum creatinine was above 120 µmol/l [11] (normal range 53–97 and 44–80 µmol/l for males and females respectively).

Mean age of death was compared for pedigree members with and without ADPKD who died between 1960 and 1995. Known historical ADPKD cases included patients for whom definite ADPKD diagnosis was known in the kindred and subjects whose position in the pedigree defined them as ADPKD cases. Reciprocally, subjects known not to have the disease were identified on the basis of a position in the pedigree which excluded the possibility to have the disease or on negative investigations. Subjects which could not be categorized as definite cases or non-cases were excluded in this survival analysis. Age of death was also assessed in an independent sample of individuals who died during the same period. This sample included 105 subjects from the Civil Status register, selecting randomly three fatalities each year between 1960 and 1995.

The proportion of all identified cases in the entire population estimated the prevalence of the phenotypically expressed disease. We used the prevalence of ADPKD cases in the middle-aged population (25–39 years) to estimate the prevalence of the carriers of the ADPKD gene(s). Indeed, most carriers of the mutant gene(s) in this age group have expressed clinical features of the disease while very few have yet died of it. Alternatively, we calculated half the number of subjects at risk in all pedigrees to estimate the prevalence of the gene(s) for ADPKD. Population figures came from a national census in 1994 [8]. Student's *t*-test was used to compare means between two groups. Exact binomial 95% confidence intervals were calculated for prevalence estimates.

Results

During the 3-year study period, a total of 42 cases of ADPKD living in the Seychelles were identified. Thirty-nine had typical ultrasonographic findings and family history and were distributed among six families, the largest with 22 cases (Figure 1). Three additional cases had negative family history but positive post-mortem (1 case) or typical ultrasonographic (2 cases) findings. The relatives of these three isolated cases had negative ultrasonography, but one father could not be investigated as he had died of an accident several years ago. In the 42 cases, age ranged from 12 to 73 years, with mean age of 35.5 years (SD 13.9). Twenty-five patients were females and 17 males. The ethnic distribution was Caucasian in 33, mixed in 8, and African in 1.

The 3-year prevalence of clinically expressed ADPKD in the Seychelles is reported in Table 1. In

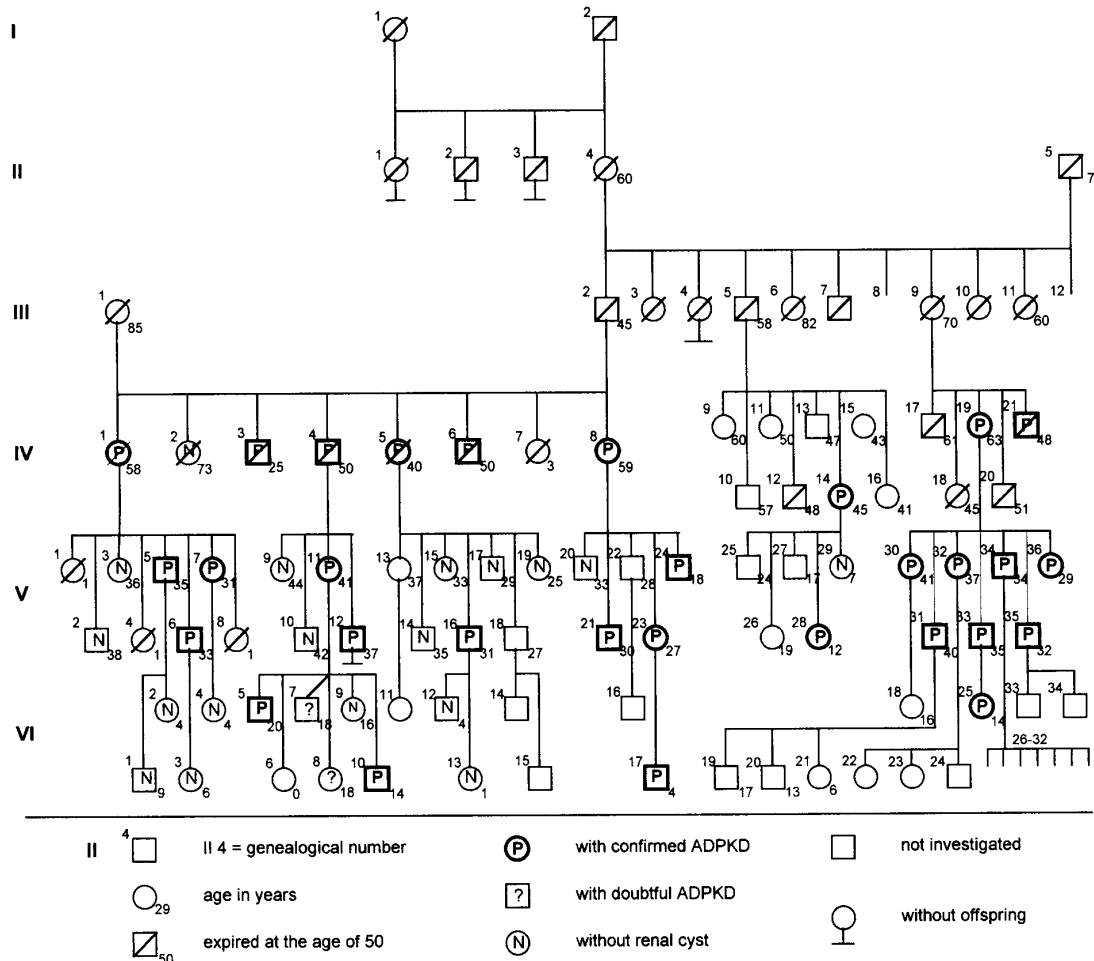


Fig. 1. Pedigree of a family with autosomal dominant polycystic kidney disease. II 4 is likely to have the disease as there is no ADPKD in the families of siblings of II 5. Marriage of I 1 and I 2 in 1864.

the mixed ethnic subgroup, we were able to assess that the disease was inherited from Caucasian parents in all cases. Therefore individuals of mixed descent were subsequently grouped with individuals of Caucasian descent when examining ethnic specific prevalence estimates. This aggregation, however, results in prevalence underestimates in the population of Caucasian descent as about one-half of the genetic material of individuals of mixed origin is not of Caucasian origin, and as this proportion is even lower considering that individuals of mixed origin also include individuals of non Caucasian descent (provided prevalence rates in the population of Caucasian descent are therefore conservative estimates). Ethnic-specific prevalence reported in Table 1 shows that the prevalence of the disease was much larger in subjects of Caucasian compared to African descent. ADPKD was not found in subjects of Asiatic descent.

The prevalence of the carriers of gene(s) responsible for ADPKD is reported in Table 1. The prevalence of the gene(s) carriers based on the number of clinically expressed disease in individuals aged 25–39 may slightly underestimate the true prevalence as three subjects at risk in this age class declined investigations

and were not accounted for in our calculation. Similarly, the prevalence of the gene(s) carriers calculated on the basis of at-risk subjects is a slight underestimate as the three isolated cases were not included in this calculation. Noticeably, the total number of subjects with clinically expressed disease ($n=42$) is expectedly smaller than the estimated number of carriers of the ADPKD gene(s) ($n=59$, using half of at-risk subjects in pedigrees) as 35 of 118 at-risk subjects (particularly the youngest) declined investigations and as many gene(s) carriers (particularly the youngest) may not have yet developed detectable cysts.

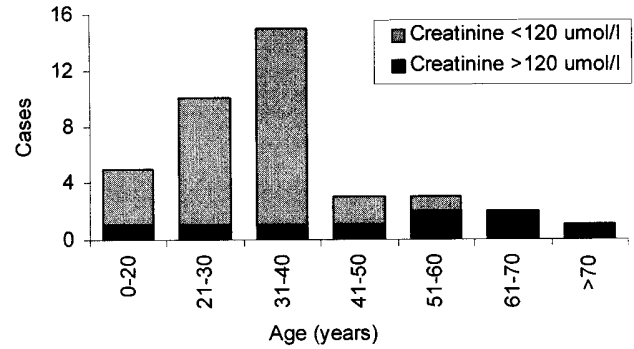
DNA was available from most alive members of family A (Figure 1) and two unconnected families. A common haplotype between markers KG8 and SM7 was shared by all affected individuals in all three families. The frequency of the different alleles for these two microsatellites is unknown in the Seychelles population. However, based on the frequency found in the DNA of the spouses, it could be different from the general population and quite high. Of the seven spouses available for the DNA study, four showed the same haplotype by chance.

Among the members of the established pedigrees,

Table 1. Prevalence of clinically expressed ADPKD and of carriers of the gene(s) responsible for ADPKD by ethnic group

	Total population			Population of Caucasian descent			Population of African descent		
	Number	Population	Prevalence*	Number	Population	Prevalence*	Number	Population	Prevalence*
Clinically expressed disease	42	74 331	57 (41–76)	41	22 299	184 (132–249)	1	48 315	2.1 (0–11)
Gene(s) carriers	19	25 481	75 (45–117)	18	7 644	236 (140–372)	1	16 563	6.0 (0–33)
Clinically expressed disease in 25–39 age group	59	74 331	79 (60–102)	59	22 299	265 (202–341)	0	48 315	0

*All prevalence estimates per 100 000; 95% CI in parentheses.

**Fig. 2.** Distribution of ADPKD cases by age and renal function.**Table 2.** Mean (SD) systolic and diastolic blood pressure in ADPKD cases and in a random sample of the general population, by age

Age category	25–34	35–44	45–54	55–64
No. of ADPKD cases	15	11	4	4
No. in general population	228	270	290	293
Systolic				
ADPKD	135 (13)*	152 (37)*	147 (29)	171 (25)*
General population	119 (16)	128 (18)	137 (25)	144 (25)
Diastolic				
ADPKD	88 (8)*	100 (23)*	90 (4)	108 (13)*
General population	78 (12)	85 (14)	88 (15)	90 (14)

* $P < 0.05$ comparing blood pressure between ADPKD cases and general population in the corresponding age group.

mean age of death occurring between 1960 and 1995 was significantly lower for the 15 cases known to have ADPKD (mean 50.5; years 95% CI: 43.1–56.9) compared to the nine cases known not to have ADPKD (67.7; 95% CI: 60.2–75.2). Among the 15 cases with ADPKD, the cause of death was chronic renal failure in five, cerebrovascular accident in one, and unspecified in 10. During the same period, the age of death in the random sample of the general population selected from the Civil Status Data was 65.8 years (95%; CI: 62.3–69.3). As haemodialysis was introduced in Seychelles in 1992, these figures mostly indicate the survival loss due to ADPKD when haemodialysis was not available.

Renal failure was found in nine (21%) of 42 subjects (serum creatinine range 127–561; mean 284; SD 144 $\mu\text{mol/l}$). Renal failure was found in one subject as young as 18 and in all four patients above age of 58 (Figure 2). Mean systolic and diastolic blood pressure was substantially higher in ADPKD cases (half of them were on antihypertensive medication) compared to individuals in the general population (Table 2).

Discussion

In this population-based study, the prevalence of ADPKD was considerably higher in Seychellois of Caucasian compared to black African descent, with all

ADPKD cases in individuals of Caucasian descent with the exception of one case in a black patient. The prevalence of clinically expressed ADPKD among the Caucasian population of Seychelles was 1:544 (95% CI: 390–736) in contrast to prevalence rates, for example, of 1:2459 in Wales [16], about 1:1000 in USA and Denmark [1,7], or 1:1111 in France [17]. Clustering of ADPKD in the Caucasian population of Seychelles could indicate a founder effect [18]. Indeed, the ADPKD gene(s) may have been introduced in Seychelles by one (or more) Caucasian(s) individual(s) among the few Caucasian and African settlers, and conserved within the Caucasian community, as interracial marriage has long been uncommon in this insular environment. In addition, haplotype analysis performed in three families showed a common DNA fragment in all affected individuals. This most probably represents a founder effect in this isolated population. However, the affected haplotype is not uncommon in the studied population and therefore the haplotype analysis should be extended to a larger DNA region before the founder hypothesis can be sustained. Alternatively, determination of the molecular mutation(s) in these families will tell how many settlers carried the disease in the Seychelles islands.

In our study, substantial underdetection of ADPKD cases due to missed families or isolated cases was unlikely as the mechanism to detect ADPKD patients and affected families involved all doctors of a small country during a long period. Routine medical examination at the tertiary, secondary, and primary health-care levels was expected to gather a substantial number of ADPKD cases, particularly considering that ultrasonographic examination to investigate hypertension and renal failure is a common medical practice in the country. Underestimate of isolated ADPKD cases was unlikely to be substantial as the proportion of isolated compared to family cases in our study (3 vs 39) was similar to or higher than figures in other populations [2,16,17]. Interestingly, the prevalence of ADPKD gene(s) estimated by ultrasonographic diagnosis in the age class 25–39 compared closely to the expected prevalence as calculated on the basis of the number of at risk subjects in the same age group (75 vs 79 per 100 000), which suggests that the ultrasonographic diagnostic criteria of Ravine used in this study were suitable to detect the disease in the Seychelles population [12].

ADPKD seemed to be exceptional in the black Seychellois population, with the disease found in only one black subject (which does not rule out Caucasian inheritance of the gene). This low prevalence in the black population was unlikely to be biased by selective survival, as ADPKD does not affect fertility due to the late onset of severe complications. Additionally, a race differential detection of ADPKD cases was unlikely, as access to medical care was available and free of charge to all inhabitants as part of a national health system. It is unclear whether prevalence of ADPKD is low in other black African populations. We found only two reports about ADPKD in black

African countries over the last 29 years: twenty-nine cases were collected over a period of 7 years in Senegal [19] and cases were reported in Ethiopia but prevalence of the disease was not specifically studied [20]. In contrast, incidence of end-stage renal disease as a consequence of ADPKD was comparable in American black and white patients undergoing dialysis [21] which may suggest that the disease affects both races similarly, at least in North America. Consequently, the generalization of our results to other populations, whether Caucasian or African, should be drawn cautiously. Further studies are needed to clarify the frequency of ADPKD in other African populations.

In Seychelles, age of death was 50.5 and 67.7 years in subjects with and without ADPKD respectively, representing a loss of 17.2 years for ADPKD cases. Noticeably, these findings applied for an epoch where dialysis was not available for management of end-stage renal disease (haemodialysis was introduced in Seychelles in 1992). A similar loss in survival was found in Canadian ADPKD patients in whom a loss of 14.8 years was observed between age of death in unaffected subjects and age of death or onset of end-stage renal disease in ADPKD patients (therefore no improved survival due to dialysis was apparent) [11]. These results suggest that the magnitude of the survival loss due to ADPKD is as large in developing countries (at least in those with middle income) as in developed countries, irrespective of life expectancy in the general population.

In the Seychelles, nine (21.4%) of 42 ADPKD patients had some degree of renal failure and three out of these nine patients had end-stage renal failure. ADPKD appeared as frequent and its prognosis as bad in Seychelles as in other countries [22–25]. For example, all four patients aged more than 58 years had serum creatinine higher than 215 $\mu\text{mol/l}$ (2.43 mg/dl) and one of these patients died of renal failure during the study period, which is consistent with the finding reported by Gabow [2] that approximately 45% of patients have end-stage renal disease by the age of 60 years. Renal failure in ADPKD has been reported to occur as early in life as 2 years of age [2] and it indeed was found in our series in a patient aged 18.

Mean systolic and diastolic blood pressure was substantially higher in ADPKD patients (half of them being treated for hypertension) than in the general population, irrespective of age. This difference may be an underestimate as blood pressure measured at the occasion of a single screening session may result in artificially high values. This finding is consistent with reports that 16% of children with ADPKD under the age of 18 had blood pressure above the 95th percentile [26] and 75% of patients aged more than 60 years had hypertension [11]. Notably, hypertension in ADPKD develops often independently of renal function impairment [11,27,28]. No evidence exists to indicate that treatment of hypertension will delay the progression of renal failure in ADPKD, but control of hypertension prevents cardiovascular morbidity and mortality [29]. Although hypertension is very common in the black

population of Seychelles [15], ADPKD cannot account for a substantial number of hypertension cases, as the prevalence of ADPKD is very low in this ethnic group.

As offspring of an affected parent has a 50% risk of inheriting the disease, a precise and factual genetic counselling can be provided. The impact of this measure may, however, be limited as far as the application of prenatal diagnosis procedures is concerned. Indeed, in a study on the attitudes of at-risk and affected individuals regarding presymptomatic testing for ADPKD, 65% of ADPKD patients indicated that they would utilize a genetic test to determine the genetic status of an at-risk fetus, but only 8% of them stated that they would terminate a pregnancy for ADPKD [30]. Case management of ADPKD should first focus, particularly in countries with limited resources, on early detection and adequate control of hypertension as these measures are relatively simple and inexpensive and are associated with improved cardiovascular outcome [31,32]. Although haemodialysis and kidney transplant are effective for long term treatment of end-stage renal failure in ADPKD [33], the use of these expensive and sophisticated techniques must be balanced with the use of scarce resources toward competitive health needs.

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