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Prevalence and Renal Prognosis of Diagnosed Autosomal Dominant Polycystic Kidney Disease in Japan

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Abstract

The prevalence and renal prognosis of diagnosed autosomal dominant polycystic kidney disease (ADPKD) in Japan were estimated. Hospital-based nationwide surveys were conducted in 1995. The number of ADPKD patients who visited hospitals but were not on chronic dialysis was estimated to be 10,000 (95% confidence interval: 8,200–11,900) and that of ADPKD patients on dialysis was 4,590, yielding a prevalence of ADPKD of 117 per million population at the end of 1994 (95% confidence interval: 102–132). The prevalence increased with age and reached a peak value of 261 per million population at the age group of 55–59 years. The rate of end-stage renal disease among living patients was calculated based on the assumption that the prevalence of ADPKD in the population under the age of 55 years was 261 per million population. The rate of end-stage renal disease increased with the progression of the patients' age, reaching 49% at the age of 65–69 years and declining thereafter. **Conclusion:** The hospital-based prevalence of ADPKD is lower than the autopsy-based prevalence, suggesting that a fairly large number of these patients do not receive medical care in their lifetime. The probability of end-stage renal disease is at most 50% among ADPKD patients who visit a hospital.

Key Words

Autosomal dominant polycystic kidney disease
Dialysis therapy
Kidney function

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary disorders [1, 2]. The incidence of ADPKD among new patients with end-stage renal disease in Japan has been about 2.9% over the last 10 years, according to the registry of the Japanese Society for Dialysis Therapy. However, the prevalence of ADPKD among the general population in Japan and the prognosis of renal function in ADPKD patients are not known. The most important outcome of ADPKD is end-stage renal disease (ESRD). Fick et al. [3] reported that 77% of ADPKD patients died after reaching ESRD and that the causes of death were intimately related to renal manifestation. Few studies have been conducted to examine the prognosis of renal function using a large number of ADPKD patients [4]. The present study was performed to clarify the prevalence of ADPKD patients among the general Japanese population and the renal prognosis of this disease.

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Method

A nationwide epidemiological survey of ADPKD patients was performed in two phases, in 1993 and 1995, respectively, as a joint study conducted by two research committees: the Research Program of Progressive Renal Disease and the Research Program on the Epidemiology of Diseases, both funded by the Ministry of Health and Welfare of Japan.

In the 1993 survey, questionnaires were sent to all hospitals in Japan with 200 or more beds. The questionnaire items included the ADPKD patients' characteristics and other detailed clinical data. Responses were collected from 1,082 ADPKD patients without dialysis. The age distribution of the 1,082 patients was applied for the estimation of the age distribution of all ADPKD patients without renal replacement therapy.

The 1995 survey was conducted to estimate the number of ADPKD patients who visited hospitals in 1994 but not for renal replacement therapy. Departments of nephrology and urology and, in the hospitals without such departments, the departments of medicine were randomly selected by the stratified sampling method from all the hospitals listed in the Ministry of Health and Welfare registry. The sampling rates were 5, 10, 20, 40 and 80% for the strata of general hospitals with less than 100 beds, 100–199 beds, 200–299 beds, 300–399 beds and 400–499 beds, respectively. Hospitals with 500 beds or more and university hospitals generally had either a nephrology or a urology department, and they were surveyed with 100% coverage. Altogether, 2,413 institutions were selected. The questionnaire, which simply inquired as to the number of patients with ADPKD who visited the hospital in 1994 and their sex and history of renal replacement therapy, was mailed in January 1995. The same questionnaire was mailed in March 1995 to the departments that had not responded by the end of February 1995.

The number and age data for ADPKD patients on dialysis therapy were obtained from the registry of the Japanese Society for Dialysis Therapy for 1994. This registration is renewed every year, and the 1994 registration covered 99.8% of the facilities engaging in dialysis therapy.

The number of patients who received a kidney transplantation was not used because only 63 Japanese ADPKD patients received a kidney transplantation between 1964 and 1990 (average, 2.3 patients/year) [5].

The method of estimating the annual number of patients surveyed by this protocol is described elsewhere [6]. Briefly, the estimation is based on the assumption that the patient number does not differ among hospitals irrespective of their response to the questionnaire. The rates of 'duplicated cases' (D) and that of 'inappropriate cases' (I), which were obtained by the first survey in 1993, were used to correct that total number, i.e. the number was multiplied by [1– (D +)I)]. 'Duplicated cases' represent a single patient reported by two or more medical facilities, and 'inappropriate cases' are patients who had not visited a hospital in 1994 or those who were not regarded as having ADPKD.

Results

Annualized Change in the Number of ADPKD Patients on Dialysis Therapy

Table 1 shows the annualized changes in the number of patients on dialysis therapy from 1986 to 1994. Throughout this period, more than 99% of the patients on dialysis therapy were registered. The taken-on rate for the renal replacement therapy of ADPKD increased during 1986–1991 but has apparently reached a plateau of 4.8 cases per million population per year over the last 4 years (row H in table 1), despite an increase in new patients as a whole (row A). As a result, the taken-on ratio of ADPKD to total patients decreased over the last 4 years from 3 to 2.5% (row C). The cumulative number of ADPKD patients as a percentage of the total cumulative ESRD patients on dialysis therapy was quite stable at around 3.2% (row F).

Estimation of Number and Age Distribution of ADPKD Patients

In the second survey, 1,253 of the 2,413 (the response rate was 51.9%) facilities replied to the questionnaire. The number of patients without renal replacement thera-

Table 1. Annualized changes in the numbers of total and ADPKD patients on dialysis therapy (DT) in Japan

		1986	1987	1988	1989	1990	1991	1992	1993	1994	Total
A	Annual number of total patients who started DT	12,565	14,784	15,512	14,374	16,543	23,005	21,563	23,440	24,059	141,786
B	Annual number of ADPKD patients who started DT	366	466	479	445	483	687	581	615	601	4,122
C	ADPKD (B/A × 100), %	2.9	3.2	3.1	3.1	2.9	3.0	2.7	2.6	2.5	2.91
D	Cumulative number of total patients on DT	66,751	80,075	83,762	84,720	95,834	114,253	121,655	131,492	142,626	–
E	Cumulative number of ADPKD patients on DT	2,055	2,510	2,714	2,739	3,183	3,816	4,000	4,304	4,594	–
F	ADPKD (E/D × 100), %	3.1	3.1	3.2	3.2	3.3	3.3	3.3	3.3	3.2	–
G	General population in Japan, × 10,000	12,095	12,154	12,203	12,246	12,272	12,404	12,445	12,476	12,503	–
H	Ratio of ADPKD patients who started DT to general population (B/G), n/1,000,000/year	3.03	3.83	3.93	3.63	3.94	5.54	4.67	4.93	4.81	–

Data are from the 'Annual Data Report' of the Japanese Society for Dialysis Therapy and the 'Annual Statistics of Japan' of the Statistics Bureau of the Management and Coordination Agency of the Japanese Government.

py was 2,572. Based on the 1,082 individual data charts of the first survey, it was judged that 1.36% cases were duplicated and 3.64% were inappropriate. After adjustment for the rates of duplicate and inappropriate cases, the number of ADPKD patients under medical care without renal replacement therapy in 1994 was estimated to be 10,000 (95% confidence interval: 8,200–11,900). The age distribution of the 10,000 patients was calculated using that of the 1,082 patients (column A in table 2).

The age distribution of the 4,594 patients on dialysis therapy in 1994 is shown in column B of table 2. Data for the age distribution by sex of these patients at the start of dialysis therapy were collected (fig. 1). The mean age was 52.3 ± 11.7 (SD) years in the men (n = 1,976) and 54.5 ± 10.7 years in the women (n = 1,723). The gender difference in mean age at the start of dialysis therapy is significant ($p < 0.001$ by the Student t test).

The total number of diagnosed ADPKD patients by age group and their ratios to the general population (prevalence) are shown in columns C and D of table 2, respectively. The average prevalence for patients of all ages in 1994 was 116.7 per million population. The prevalence increased as the age increased, reaching 261.4 per million

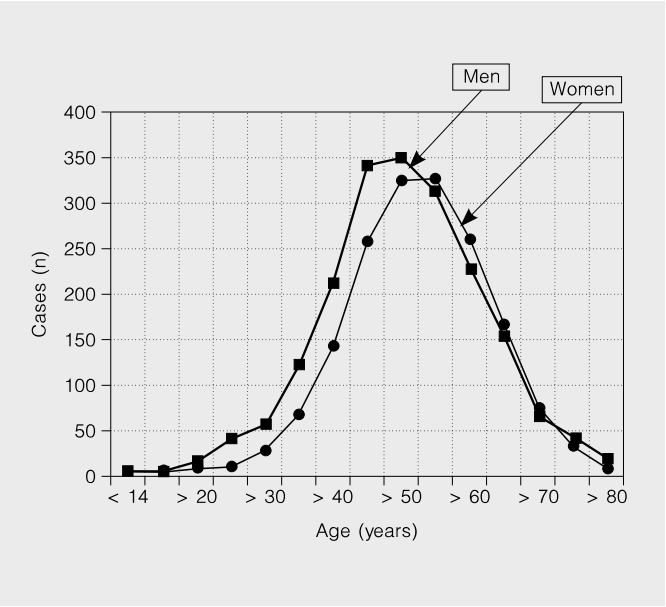

Fig. 1. Age distribution at the time patients with ADPKD had started dialysis therapy. The mean age was 52.3 ± 11.7 (SD) years in the men (n = 1,976) and 54.5 ± 10.7 years in the women (n = 1,723). The difference between the men and women in the mean age at the start of dialysis therapy is significant ($p < 0.001$).

Table 2. Age distribution of ADPKD patients and the prevalence of ADPKD in the general population

Age years	(A) Number of patients who visited hospital but were not on dialysis in 1994	(B) Number of patients on dialysis in 1994	(C) Total number of patients in 1994 (A + B)	(D) Prevalence of ADPKD in the general population n/1,000,000
0–14	92	10	102	5
15–19	120	7	127	14.3
20–24	176	7	183	18.3
25–29	268	23	291	33.6
30–34	462	37	499	63.2
35–39	869	113	982	124.1
40–44	1,377	334	1,711	180.3
45–49	1,451	460	1,911	191.5
50–54	1,460	719	2,179	240.5
55–59	1,174	878	2,052	261.4
60–64	952	829	1,781	243.3
65–69	665	631	1,296	208
70–74	481	325	806	179.5
75–79	277	165	442	140.3
>80	176	56	232	62.4
Total	10,000	4,594	14,594	116.7
(95% confidence interval: 8,200–11,900)				

The total number of ADPKD patients was obtained at the second survey in 1995, and their age distribution was derived from the 1,082 patients' data of the first survey in 1993. The number of ADPKD patients on dialysis was obtained from the Registry of the Japanese Society for Dialysis. Therapy.

Table 3. Renal prognosis of ADPKD (probability of ESRD in ADPKD patients)

Age years	(A) Prevalence of ADPKD used to estimate renal prognosis n/1,000,000	(B) General population of Japan in 1994 × 10,000	(C) Number of patients used to estimate renal prognosis a × b/100	(D) Number of ADPKD patients with dialysis therapy in 1994	(E) Probability of ESRD in ADPKD patients in 1994 (D/C ± 100), %
0–14	261	2,041.0	5,330	10	0.2
15–19	261	886.7	2,310	7	0.3
20–24	261	998.6	2,610	7	0.3
25–29	261	867.2	2,260	23	1
30–34	261	789.7	2,060	37	2
35–39	261	790.6	2,060	113	5
40–44	261	949.4	2,480	334	13
45–49	261	997.6	2,600	460	18
50–54	261	906.3	2,370	719	30
55–59	261	785.3	2,050	878	43
60–64	243	732.0	1,780	829	47
65–69	208	622.7	1,300	631	49
70–74	180	449.2	810	325	40
75–79	140	314.6	440	165	38
>80	62	372.0	230	56	24
Total	248	12,503	31,000	4,594	15

The prevalences of ADPKD patients above 55 years of age were derived from row D of table 1. The prevalence of patients aged 55–59 years was adopted as that of patients below 55 years. General population data were obtained from the 'Annual Statistics of Japan' of the Statistics Bureau of the Management and Coordinate Agency.

population in the age group of 55–59 years and decreased thereafter.

Outcome of Renal Function in ADPKD

Assuming that the ratio of ADPKD patients to the general population in the age groups younger than 55 was 261 per million population (column A in table 3), the total number of patients with ADPKD was estimated to be 31,000 (column C in table 3). This number represents the sum of all patients who were under medical care in 1994 and the patients who were under the age of 55 years in 1994 and had not yet presented themselves to a medical facility, but would survive and be diagnosed by the age of 55. This number gave a prevalence of 1:4,033 to the general population. The estimate does not include patients who remain undiagnosed in their lifetime and those who had died before this survey in 1994. Using these numbers, the rate of ESRD was estimated (column E in table 3). The probability of ESRD increased as age increased and reached the highest rate of 49% at the ages of 65–69 years and decreased at over 70 years of age.

Discussion

The taken-on rate for renal replacement therapy in ADPKD increased during 1986–1991 but has apparently reached a plateau of 4.8 cases per million population per year over the last 4 years. During the same period, the new dialysis patients increased as a whole, which is mainly attributed to an increase in diabetic nephropathy. The stable taken-on rate for ADPKD patients may indicate a constant proportion of ADPKD to the general population.

It is important but difficult to obtain a reliable estimate of the prevalence of ADPKD and the outcome of renal failure. The frequency of ADPKD may vary depending on the area and the race studied, the methods employed, and the time at which the study was conducted. The most basic frequency of ADPKD is that of people who have a mutation of ADPKD genes and an expressed phenotype (genetic frequency). Since mutated genes are not only transmitted in a hereditary manner but also generated by de novo mutation, and since at least three different loci are suspected for ADPKD, and since the long duplicated area in the PKD-1 region locates in

the vicinity of the PKD-1 gene [7], it is very difficult to estimate the genetic frequency among the general population at the present time. The frequency of ADPKD obtained by autopsy studies may be close to the genetic frequency, but it is also difficult to carry out an autopsy study in a manner that avoids death-cause-related bias. Hospital-based autopsy studies have a bias because ADPKD patients may be more frequently accumulated in those studies. The frequency of ADPKD reported by ten separate autopsy studies which were summarized by Dalgaard [8] varied from 1 per 222 to 1 per 1,019 persons. The combined figure for the ten studies was 1 in 492. Recent autopsy studies in Hong Kong Chinese and in Heidelberg Germans revealed approximately 1 ADPKD patient in 340 autopsies [9, 10]. Therefore, the frequency of ADPKD obtained by hospital-based autopsy studies was around 1 in 300 to 1 in 500.

The frequency of ADPKD estimated in a hospital-based study includes two figures. One is the frequency of ADPKD patients among hospital admissions and the other is the prevalence of ADPKD among the general population. The ADPKD patient frequency among hospital admissions was from 1 per 2,438 to 1 per 4,933 in general hospitals and 1 per 342 in urology clinics [8]. The frequencies of ADPKD patients among hospital admissions were apparently lower than the frequency obtained by autopsy.

Few hospital-based epidemiological studies have estimated the prevalence of ADPKD among a general population. The hospital and autopsy combined survey in Olmsted County, Minn., USA, identified 40 clinical and 32 autopsy cases (the autopsy cases included 16 actually identified cases and 16 estimated cases had a 100% autopsy been performed) between 1935 and 1980 [11]. The annual incidence rate was estimated as 1.38 per 100,000 person-year. This study was performed on a uniquely defined community population and the results are applicable for the estimation of the annual incidence rate among white Americans. However, the study did not reveal the prevalence of ADPKD.

There are two hospital register-based epidemiological studies that have estimated the frequency of ADPKD in a general population. A study in Copenhagen, Denmark, indicated that the morbidity risk of ADPKD up to the age of 59 years was 522 in women and 562 in men per million population during 1935 and 1953 [8]. These figures give the prevalence of 1:1,915 in women and 1:1,779 in men. A study in South and Mid-Wales in the UK revealed an apparent prevalence of ADPKD of 1:2,459 in the general population, a prevalence which included predicted family members at 50 and 25% risk [12]. The method of these studies is similar to that of the present study, but the Wales and Copenhagen studies included unsearched predicted family members. The present study was based solely on hospital admissions and is more closely related to the number of patients who received medical care. The prevalence of the present study is 1:4,033, a figure which is approximately half of those obtained in the above studies which included family members.

In the Wales study, the take-on rate for renal replacement therapy reached a plateau of 4.8 cases per million population per year in 1980–1989. In Japan, the rate reached a plateau around 4.7–5.5 cases (table 1) for recent years. The plateau rate of new patients who start renal replacement therapy has been similar between Japan and Wales in recent years.

The fact that the prevalence (1:2,000 to 1:4,000) of ADPKD estimated based on hospital admissions [8, 12 and present study] is lower than that (1:300 to 1:500) obtained by autopsy studies [8–10] indicates that a fairly large number of ADPKD patients are asymptomatic or are not symptomatic enough to seek medical attention.

The renal prognosis (column E in table 3) was found to be better at ages over 70 years in the present study. The reason is presumably that the patients who survive over 70 years have a better renal function than those who died before 70. In table 4, data regarding the prognosis for patients with ADPKD in several countries [4, 13–16] are tabulated and compared with those of the present study. It is intriguing that relatively similar results were obtained although different methods were used in the previous [4, 14–16] and present studies. The prognosis generally improved in the later studies, probably due to better medical management, early diagnosis, diagnosis of patients with mild phenotype and other improvements in environmental factors. In a study published in 1977, it was estimated that 70% of the patients would reach ESRD if they survived to the age of 65 years [17]. This probability is considerably higher than that (47%) found in the present study. The recent extensive study by Gabow et al. [4] disclosed a low probability of ESRD. Their results are relatively similar to that of the present study at ages less than 58 years, but showed a higher probability at the age of 70. This variance may reflect a better prognosis for the patients who had survived over 70 years in the present study, and the comparison over 70 years may have no importance.

The validity of the data of ADPKD patients on dialysis should be emphasized, because the patient registration of the Japanese Society for Dialysis Therapy is highly thor-

Table 4. Comparison of reported data for probability of ESRD in ADPKD

Authors/year	Ref. No.	Patients	Country	Age group years	Probability of ESRD, %	
					probability	present data
Milutinovic et al. 1984	14	140	USA	by 40 40–49 over 50	5 33 47	5 (35–39 years) 16 (40–49 years: 794/5,080) 40 (over 50 years: 3,603/8,980)
Churchill et al. 1984	15	140	Canada	by 50 by 58 by 73	23* 43* 48*	18 (45–49 years) 43 (55–59 years) 40 (70–74 years)
Gonzalo et al. 1990	16	107	Spain	by 50 by 58 by 70	26* 49* 63*	18 (45–49 years) 43 (55–59 years) 49 (65–69 years)
Gabow et al. 1992	4	580	USA	at 50 at 58 at 70	29 47 77	30 (50–54 years) 43 (55–59 years) 40 (70–74 years)

* = The probability of being dead or having ESRD; numbers without an asterisk indicate the probability of having ESRD for a patient who survives to the age indicated. Figures in parentheses indicate age groups.

ough and includes almost all of the patients who have been on dialysis for more than the past 10 years. The present study estimated the renal prognosis based on the number of ADPKD patients who are diagnosed during lifetime. The number of ADPKD patients diagnosed during lifetime is roughly half of the total patients, because it was reported that undiagnosed patients (diagnosed by autopsy only) are roughly equal in number to clinically diagnosed patients during lifetime [12]. If lifetime undiagnosed patients are included in the present study, the estimation of renal prognosis would become much better because the denominator (total ADPKD patients) would be doubled while the numerator (dialysis patients) would remain unchanged.

In conclusion, the prevalence of diagnosed ADPKD is 1:4,033 among the general Japanese population. This prevalence is approximately half of those in the previous studies which included predicted family members. The prevalence of diagnosed ADPKD is roughly one tenth of the autopsy-based prevalence, suggesting that a fairly large number of ADPKD patients do not receive medical care in their lifetime. The probability of ESRD is at most 50% among ADPKD patients diagnosed by the age of 69 years. The renal prognosis estimated in the present study is slightly better than that reported previously. The possibility to explain the better renal prognosis such as different distribution of ADPKD gene types (PKD-1 and PKD-2) between western countries and Japan is less likely because of the similar renal prognosis of ADPKD patients in the USA [4] and Japan and the similar take-on rates for renal replacement therapy between Wales and Japan. In addition, our preliminary study showed a rate of PKD-1-gene-related family almost identical to those of western countries [18].

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