Mortality Associated with Polycystic Kidney Disease

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Introduction.

Autosomal dominant polycystic kidney disease (ADPKD, McKusick's catalog number 17390, 1986[1]) is one of the commonest monogenetic disorders, with an estimated frequency of about 1 in 1,000, essentially complete penetrance, but variable clinical presentation with onset at an average age of about 40 years.[2,3]

The pathogenetic processes involved in the progressive development of renal cysts, leading to terminal uremia, are still unknown.

As for the general symptomatology, progressive clinical development, and age of diagnosis they have not changed significantly during the last 30 years (Tables 1 and 2).

In 60% of Dalgaard's 350 cases (1957) the clinical diagnosis had still not been made at the age of 45 years.[2] Bear *et al.* (1984) report similarly.[4]

Table 1.

Number of individuals with polycystic kidneys in different age groups, when warning was given of the malformations for the first time by one or more of the various symptoms (From Dalgaard 1957[2]).

Age	Pain and abdominal symptoms	Kidney Colic passage of calculi	Protein-uria	Hema-turia	Pyuria and bacteriuria	Kidney-tumour	Cardio-vascular symptoms hypertension	Uremia symptoms	Renal insuffi-ciency
5-9	1	–	–	–	–	–	–	–	–
10-14	–	–	2	1	–	–	–	–	–
15-19	6	2	3	–	4	1	–	–	–
20-24	9	6	4	5	4	2	1	–	–
25-29	13	6	10	6	10	3	2	–	–
30-34	15	10	10	15	7	5	3	–	–
35-39	18	8	6	11	10	7	5	2	–
40-44	23	4	7	13	5	6	8	2	–
45-49	16	3	5	10	5	3	4	6	1
50-54	18	5	5	12	3	5	9	2	–
55-59	6	1	4	3	1	1	8	5	2
60-64	3	–	1	3	1	1	5	1	–
65-70	1	–	1	–	–	–	3	1	–
70-74	2	–	1	1	–	–	5	1	1
75-79	1	–	–	–	–	–	1	1	–
Women	88	21	34	33	44	25	26	13	1
Men	44	24	25	47	6	9	28	8	3
Totals	132	45	59	80	50	34	54	21	4

Table 2.

Probability of Clinical Diagnosis of Adult Polycystic Kidney Disease

Age	Dalgaard 1957[2] %	Bear *et al.* 1984[4] %
25	5	3.8
35	17	16.4
45	40	41.0
55	70	69.4

However, the prognosis and life expectancy of affected individuals have improved due to the progress in the treatment of complications such as urinary tract infections and calculi, hypertension and cardiac insufficiency, let alone the development of hemodialysis and kidney transplantation. ADPKD currently accounts for 10% of kidney transplantations in Denmark. Furthermore, the development of ultrasonography has made early presymptomatic diagnosis possible, and recent advances in molecular biology now allow a still earlier evaluation of carrier status by DNA analysis. For embryos with ADPKD-gene prenatal diagnosis of ADPKD can be made in 95% of the cases.[5]

Gene localization.

The gene for ADPKD (locus-symbol PKD1) has recently been assigned to the short arm of chromosome 16, by demonstration of linkage to the TK-globin gene cluster, in a genetic distance of about 5 centimorgan.[6,7] This was accomplished by use of the highly polymorphic DNA market 3' HVR.[8,9]

Subject studied.

242 adults with bilateral polycystic disease of the kidneys were ascertained from the hospitals of Greater Copenhagen during the period 1920-1953.

For the deceased the death certificates and possible hospital records were traced.

The author examined the living and all their closer living family members in Denmark including clinical history, physical examination, blood pressure, urine examination, kidney function test and intravenous urography.

The total material comprises a clinical analysis of the course of the disease in 350 certain cases of ADPKD, 157 men and 193 women.

Table 1 shows the ages at which ADPKD was first manifest by one or more of the various symptoms, which seldom appear during the first two decades.

The mean age at onset of the disease established by one or more symptoms was 40.7 years, 41.6 years for males, 39.9 years for females, and varying from 8 to 77 years.

The mean age of the time of diagnosis was 47.2 years, one year earlier for the females than for the males and varying from 16 to 85 years.

In Bear *et al.* (1984)[4] the probability that cases with ADPKD had been diagnosed by the ages 25, 35, 45 and 55 years are nearly identical to my calculations of 1954 — 30 years earlier (Table 2).

Follow up.

At the time of follow-up 254 patients were deceased, the average age of death was 51.5 years, identical for males and females, in contrast to 71 years among the general Danish Population.

59% died from uremia, 13% from cerebral hemorrhage, 6% from heart disease and 22% from other causes (Table 3).

In the case of the 96 living patients, 43 males and 53 females, the average age was 45.7 years and thus less than in the case of the deceased, due to the fact that almost a third were diagnosed by the author himself when they were at a young age, with limited exposure for risk of death up to 1953, the end of follow-up.

Results.

At the suggestion of Richard B. Singer, MD, all the 350 patients were considered as a cohort with mortality and survival by annual periods of attained age. With the retrospective exposure (Table 4) all the patients were age 20 at the time of entry into the life table as there were no deaths observed under that age.

The patients were separated into male and female cohorts.

Table 3.

Causes of death in relation to age at death for 173 patients with polycystic kidneys (only autopsies), divided into 10-year groups.

Cause of death	20-29	30-39	40-49	50-59	60-69	70-79	80-	in all	in all %
Uremia	1	10	33	37	18	4	1	104	60
Cerebral Hemorrhage	2	2	10	6	3	1		24	14
Heart death	0	1	1	4	1	2		9	5
Other causes	1	1	7	16	7	3	1	36	21
Totals	4	14	51	63	29	10	2	173	100

Table 4.

Comparative Mortality in Polycystic Kidney Disease by Attained Age 20 *

Attained Age x to x+Δx	No. Alive at Age x* l	Withdrawn Alive w	Exposure Pt-Yrs E	No. of Deaths Observed d	No. of Deaths Expected+ d'	Mortality Ratio 100d/d'	Mean Ann. Mort. Rate/1000 Observed q=d/E	Mean Ann. Mort. Rate/1000 Expected q'	Mean Ann. Mort. Rate/1000 Excess (q-q')
				Male Patients					
20-29	156	4	1537.0	3	2.00	150%	2.0	1.3	0.7
30-39	149	12	1408.0	13	2.37	550	9.2	1.7	7.5
40-49	124	14	1009.0	36	3.73	965	36	3.7	32
0-59	74	6	519.0	39	5.09	765	75	9.8	65
60-69	29	6	183.0	15	4.43	340	82	24	58
70-83	8	1	55.5	7	3.61	194	126	65	61
20-83	156	43	4711.5	113	21.23	530	24	4.5	20
				Female Patients					
20-29	193	2	1920.0	3	1.35	220%	1.6	0.7	0.9
30-39	188	17	1742.5	15	2.44	615	8.6	1.4	7.2
40-49	156	10	1318.0	45	4.09	1100	34	3.1	31
50-59	101	16	725.0	45	5.22	860	62	7.2	55
60-69	40	5	248.5	24	4.55	530	97	18	79
70-79	11	3	50.5	8	2.39	335	158	47	111
20-79	193	53	6004.5	140	20.04	700	23	3.3	20

* Retrospective exposure to age 20 assumed valid: excess mortality very small < age 35
\+ Basis of expected deaths: 1951-55 Danish Life Tables

Exposure was calculated in person-years from entry at age 20 until age of death for the 254 fatal cases or the age of follow-up for the 96 survivors.

Comparative mortality was derived from 1951-55 Mortality Table for the Danish Population, with calculation of d' as the product of E and age/sex-specific values of q'.

Mortality experience is extremely high, mortality ratios averaging 600% in that of the Danish Population for ages 30-39 years rising to more than 900% for ages 40-59 years, but diminishing to 350% for ages over 60 years. The higher mortality ratios in females are attributable to lower q' rates rather than higher observed q values.

A mortality ratio (MR) of 350% at ages 60 up is extremely high in terms of excess death rate (EDR).

Excess deaths per 1,000 (EDR) for males are quite low under age 35, however increase from 16 for ages 35-39 to about 60 at ages 50 up.

For females the excess deaths per 1,000 continue to increase at ages 50 up, exceeding 100 in the oldest age group.

Comments

The use of retrospective exposure prior to diagnosis can be justified in an inherited disease that is progressive in severity (homochronous). The method has been used in some types of congenital heart disease (see Abstract 332 in *Medical Risks* 1976).

The combination of a rather late development of incapacitating clinical manifestations, and a dominant mode of inheritance, explains the frequent propagation of the disease for many generations of affected families. When, furthermore, the incidence of ADPKD is as high as about 1 in 1,000, there is a sizeable need for preventive measures, if possible, for those families who desire to have only unaffected children.

Early detection of asymptomatic carriers became possible with the development of urography, and especially ultrasonography which is a harmless, non-invasive and fast procedure with a high degree of sensitivity. By this analysis polycystic kidneys, and liver, can be visualized 10-15 years before the onset of clinical symptoms, i.e., the diagnosis can be established in about 85% of the actual carriers at the age of 25 years.[4]

DNA marker analysis has greatly improved the early delineation

of carriers and non-carriers among at-risk individuals, including the early fetus, and has thus become a valuable tool for the prevention of propagating ADPKD in affected families.[10,11]

The high morality rate of ADPKD patients is reflected in the policies recommended for Life Insurance Companies (Brackenridge 1985[12]). Applicants with known polycystic kidney disease must be declined. For applicants with a family history of ADPKD it is suggested that the insurance company should as a rule only consider individuals who have reached the age of thirty or more. Applicants with a recent normal ultrasonography can be considered for life insurance at the age of 25 years, with a temporary extra premium ceasing at the age of 35. If reliable ultrasound scanning is normal at or above age 35 years, the individual can be insured at standard premium rates.

One has to realize that the recent development in predictive DNA analysis for ADPKD, and other genetic diseases manifesting in adulthood, is bound to have an impact on insurance strategies.[13]

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