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Mortality Rate of Amyloidosis in Japan: Secular Trends and Geographical Variations

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The death rate in Japan from amyloidosis was analyzed using Japanese Vital Statistics for 1969–1985. The amyloidosis death rate has increased gradually year by year for both sexes. The changing patterns in mortality might be explained by a constantly improving ascertainment of amyloidosis. The overall amyloidosis death rate per 100,000 of the population was 0.06 during the period from 1969 to 1978. The geographical variations in the amyloidosis death rate were observed with the highest death rate in Kumamoto and Nagano prefectures (0.29 per 100,000 population) for both sexes during the period from 1979 to 1985. The amyloidosis death rates (per 100,000 population) in 2 large foci of familial amyloidosis polyneuropathy were 9.4 in Ogawa Village, Nagano Prefecture and 3.5 in Arao City, Kumamoto Prefecture during the period from 1979 to 1985. The mean age at death from amyloidosis gradually increased year by year for both sexes, although the age was 11–23 years shorter for males and 20–25 years shorter for females than that of the general population.

KEY WORDS: **familial amyloidosis polyneuropathy, vital statistics, mean age at death**

INTRODUCTION

Amyloidosis is a mixture of diseases. Deaths certified as caused by amyloidosis include many with inherited systemic amyloidosis, secondary amyloidosis, familial Mediterranean fever, and others. According to McKusick [1988], hereditary amyloidosis can be classified into 9 types: amyloidosis I to IX. Familial amyloidosis polyneuropathy (FAP) corresponds to amyloidosis I of McKusick [1988]. According to Ikeda et al. [1987], the most common form of hereditary generalized amyloidosis in Japan is FAP. There are 2 large foci of FAP: the Arao district in southern Japan [Araki et al., 1968; Sakoda et al., 1983] and Ogawa Village in Central Japan [Kito et al., 1973; Itoga and Kito, 1982]. According to Itoga and Kito [1982] and Sakoda et al. [1983], FAP in the above 2 areas was transmitted as an autosomal dominant trait in the same way as in Portuguese and Swedish families [Andrade et al., 1969; Andersson, 1976]. Recently, it was found that the abnormal transthyretin or prealbumin in the tissues of patients with FAP in Arao city has a substitution of methionine for valine at position 30 [Tawara et al., 1983]. Yoshioka et al. [1986] determined the complete nucleotide sequence of the prealbumin gene. The same valine-to-methionine substitution at position 30 of transthyretin was found in a Swedish family with FAP [Dwulet and Benson, 1984], in a Portuguese case [Saraiva et al., 1986a], and in a Greek case [Saraiva et al., 1986b].

The present study deals with the secular changes and the geographical variations in the amyloidosis death rate during the period from 1969 to 1985 in Japan.

MATERIALS AND METHODS

Data consisting of 1,109 deaths with amyloidosis reported for 1969–1985 inclusive have been obtained from the death certificate records kept at the Ministry of Health and Welfare, Japan. The certificate includes information on sex, place of residence, dates of birth and death, cause of death, and other. Data on the general population were taken from the annual volumes of the "Vital Statistics of Japan for the Years 1969–1985" [Japan Ministry of Health and Welfare, 1971–1987], which cover the entire population of Japan.

In computing the amyloidosis death rate, the number of deaths from amyloidosis in each sex were divided by the population size of each sex during the same period. On the other hand, in computing the regional amyloidosis death rate, the population size as the denominator in each prefecture was the average of that of the two census years for 1970 to 1975 and 1980 to 1985 and of four census years between 1970 and 1985.

RESULTS

Secular Change in the Amyloidosis Mortality Rate

Table I shows secular changes in the amyloidosis death rates for each sex during the period from 1969 to

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TABLE I. Secular Change in Amyloidosis Death Rate by Sex During 1969–1985

Year	No. of deaths			Amyloidosis death rate per 100,000 population		
	Males	Females	Total	Males	Females	Total
1969	11	11	22	0.0220	0.0212	0.0216
1970	7	8	15	0.0138	0.0152	0.0145
1971	6	7	13	0.0117	0.0132	0.0125
1972	15	6	21	0.0289	0.0111	0.0199
1973	17	14	31	0.0321	0.0254	0.0287
1974	24	14	38	0.0447	0.0251	0.0347
1975	25	22	47	0.0457	0.0389	0.0422
1976	33	16	49	0.0596	0.0280	0.0436
1977	29	15	44	0.0519	0.0260	0.0388
1978	28	37	65	0.0497	0.0636	0.0568
1979	41	29	70	0.0721	0.0495	0.0606
1980	38	36	74	0.0664	0.0609	0.0636
1981	54	45	99	0.0937	0.0756	0.0845
1982	50	67	117	0.0861	0.1118	0.0991
1983	65	66	131	0.1112	0.1094	0.1103
1984	66	63	129	0.1123	0.1037	0.1079
1985	75	69	144	0.1269	0.1128	0.1197

1985. The total number of male deaths from amyloidosis was 11 in 1969 and 75 in 1985. The corresponding death rates per 100,000 of the population were 0.0220 and 0.1269, respectively. Therefore, the latter is 5.8 times higher than the former. Similarly, the total number of female deaths from amyloidosis was 11 in 1969 and 69 in 1985. The corresponding death rates per 100,000 of the population were 0.0212 and 0.1128, respectively, in which the latter is 5.3 times higher than the former. Therefore, the death rate is similar for both sexes during the period. The linear regression coefficients of the amyloidosis death rate on the year (per 100,000 years) are 0.0068 ($\pm$0.0004) for males and 0.0069 ($\pm$0.0007) for females. These values were significant at the .1% level.

Age-Specific Mortality Rate of Amyloidosis

The amyloidosis death rate has increased gradually year by year for both sexes. The age-specific amyloidosis death rates were computed during 2 periods from 1969 to 1978 and 1979 to 1985 (Fig. 1). In both sexes, the amyloidosis death rate was nearly constant up to the 25–29 year age group; it gradually increased thereafter up to the 70–74 year age group for men and the 65–69 year age group for women during the period from 1979 to 1985 and the 65–69 year age group for men during the period from 1969 to 1978, decreasing thereafter. On the other hand, the amyloidosis death rate for women during the period from 1969 to 1978 was nearly constant up to the 35–39 year age group, gradually increased thereafter up to the 45–49 year age group, again was nearly constant up to the 65–69 year age group, and decreased thereafter.

Geographical Variation

The amyloidosis death rate was computed in each prefecture during the periods from 1969 to 1978, 1979 to 1985, and 1969 to 1985 (Table II). In order to look at the geographical variations in the death rate, the coefficient of variations are computed in each period. The corresponding coefficients of variations were 0.88, 0.61, and 0.61, respectively. Therefore, the geographical variation was reduced in recent years. Overall death rates per 100,000 population were 0.032 in the former period and 0.092 in the latter period. The ratio of the death rate in the latter to that in the former was 2.9. All prefectures had these ratios in the range from 0.8 to 16.7. Accordingly incomplete ascertainment of amyloidosis in the former period was especially indicated in 6 prefectures (Tochigi, Ishikawa, Mie, Shimane, Kagawa, and Okinawa).

In the present analysis, the geographical variations in the death rate are during the period from 1979 to 1985. The highest amyloidosis death rate was seen in Nagano and Kumamoto prefectures (0.291). The amyloidosis death rate in these prefectures is 3.2 times as high as the overall amyloidosis death rate in Japan. The second highest amyloidosis death rate was seen in Nagasaki (0.260) and Saga prefectures (0.246) and was followed by Shimane Prefecture (0.217). On the other hand, the lowest amyloidosis death rate was seen in Yamanashi Prefecture (0.017), followed by Tokushima Prefecture (0.034). The regression coefficient of the amyloidosis death rate on the latitude of the prefectural capital (per 100 degree) was -0.0099 ± 0.0057, and this coefficient was not significant from zero. However, the death rate was higher in the southwest than in the northeast.

The number of deaths from amyloidosis in each prefecture were divided into each ward, city, town, and village (administrative unit) during the period from 1979 to 1985. It is called a city or town and village according to whether the population size of the administrative unit is over 30,000 or not. When the population size of a city is over 1 million, the city is subdivided into several wards. The amyloidosis death rate was computed in each area where the population size as the denominator in each area was the average of that of the 2 census years between 1980 and 1985. Figure 2 shows areas of higher amyloidosis death rate in Japan. The highest death rate was obtained in Ogawa Village, Nagano Prefecture (11.79 per 100,000 population), fol-

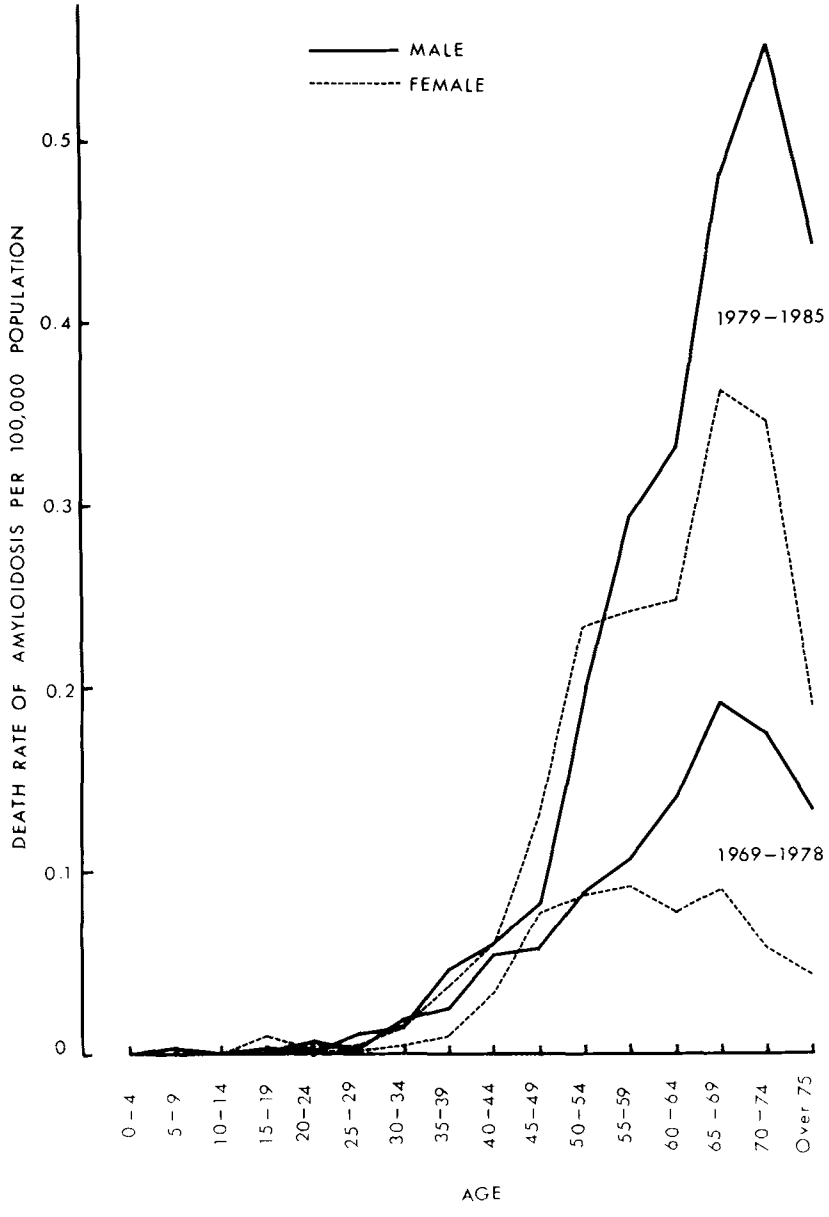

Fig. 1. Age-specific amyloidosis death rate by sex during 1969–1985.

lowed by Yasaka (9.52), Kinasa (9.39), and Nakajo villages (7.47), the latter 3 being neighboring villages of Ogawa. On the other hand, the highest death rate in urban areas (ward and city) was obtained in Arao City, Kumamoto Prefecture (3.45 per 100,000 population). As the population size of a town or village was small, the amyloidosis death rate was recomputed in each *gun* (town and village). A *gun* consists of approximately 6 towns and/or villages. The highest death rate was obtained in Kamiminochi-*gun* (2.39 per 100,000 population), followed by Shimominochi-*gun* (1.59) and Nagano Prefecture, where Ogawa, Kinasa, and Nakajo villages belong to Kamiminochi-*gun*.

Next we computed the amyloidosis death rates by ward, city, and *gun* during the period from 1979 to 1985. The total number of deaths from amyloidosis was 130 in ward, 424 in city, and 210 in *gun*. The death rate per 100,000 of the population was the highest in *gun* (0.107), followed by city (0.091) and ward (0.076). The amyloidosis death rate in urban areas was 0.087. Therefore, the death rate was higher in rural than in urban areas.

Mean Age at Death

Figure 3 shows the secular change in the mean age at death from amyloidosis in each sex during the period from 1969 to 1985. The mean age at death from amyloidosis was 46.7 years for males and 52.8 years for females in 1969–1970, and the corresponding mean age in 1985 was 60.3 years and 60.2 years, respectively. The

TABLE II. Death Rate From Amyloidosis per 100,000 Population in Each Prefecture, 1969–1978 and 1979–1985

Prefecture	No. of deaths			Death rate			(1979–1985/
	1969–1978	1979–1985	Total	1969–1978	1979–1985	Total	1969–1978)
Whole of Japan	345	764	1,109	0.032	0.092	0.057	2.9
Hokkaido	16	16	32	0.030	0.041	0.035	1.3
Aomori	5	10	15	0.035	0.094	0.059	2.7
Iwate	3	7	10	0.022	0.070	0.042	3.2
Miyagi	5	10	15	0.026	0.067	0.044	2.5
Akita	4	9	13	0.032	0.102	0.061	3.2
Yamagata	5	16	21	0.041	0.182	0.100	4.4
Fukushima	3	10	13	0.015	0.069	0.038	4.5
Ibaraki	5	14	19	0.022	0.076	0.046	3.4
Tochigi	1	9	10	0.006	0.070	0.034	11.5
Gunma	3	13	16	0.018	0.099	0.052	5.6
Saitama	7	15	22	0.016	0.038	0.026	2.4
Chiba	10	21	31	0.027	0.061	0.042	2.3
Tokyo	36	68	104	0.031	0.083	0.053	2.7
Kanagawa	20	42	62	0.034	0.084	0.056	2.5
Niigata	11	24	35	0.046	0.139	0.085	3.0
Toyama	4	7	11	0.038	0.090	0.060	2.4
Ishikaway	1	11	12	0.010	0.138	0.065	14.3
Fukui	5	9	14	0.066	0.160	0.105	2.4
Yamanashi	1	1	2	0.013	0.017	0.015	1.3
Nagano	25	43	68	0.126	0.291	0.195	2.3
Gifu	7	8	15	0.039	0.057	0.046	1.5
Shizuoka	12	18	30	0.038	0.073	0.053	2.0
Aichi	15	29	44	0.027	0.065	0.043	2.5
Mie	1	12	13	0.006	0.100	0.046	15.8
Shiga	2	8	10	0.021	0.102	0.057	4.8
Kyoto	8	17	25	0.034	0.095	0.060	2.8
Osaka	11	28	39	0.014	0.047	0.028	3.4
Hyogo	9	24	33	0.019	0.066	0.039	3.5
Nara	5	6	11	0.050	0.068	0.057	1.4
Wakayama	1	3	4	0.009	0.039	0.022	4.2
Tottori	8	5	13	0.139	0.117	0.129	0.8
Shimane	1	12	13	0.013	0.217	0.098	16.7
Okayama	5	18	23	0.028	0.136	0.074	4.8
Hiroshima	9	9	18	0.035	0.046	0.040	1.3
Yamaguchi	5	17	22	0.033	0.152	0.083	4.7
Tokushima	3	2	5	0.038	0.034	0.036	0.9
Kagawa	1	9	10	0.011	0.127	0.060	11.9
Ehime	2	10	12	0.014	0.094	0.048	6.8
Kochi	1	4	5	0.013	0.068	0.036	5.5
Fukuoka	23	42	65	0.055	0.129	0.087	2.3
Saga	6	15	21	0.072	0.246	0.144	3.4
Nagasaki	10	29	39	0.064	0.260	0.145	4.1
Kumamoto	22	37	59	0.129	0.291	0.197	2.3
Oita	2	8	10	0.017	0.092	0.049	5.4
Miyazaki	3	16	19	0.028	0.196	0.100	7.0
Kagoshima	3	11	14	0.017	0.087	0.047	5.0
Okinawa	0	12	12	0	0.150	0.072	–

mean age at death for both sexes gradually increased with time. The mean age at death was similar for both sexes after 1975.

DISCUSSION

Hayakawa and Kurihara [1984] compared amyloidosis death rates in 17 countries during the period from 1968 to 1980. The highest death rate per 100,000 of the population was in Sweden (0.39–0.63), followed in order by Finland (0.39–0.52), Denmark (0.20–0.36), and Norway (0.17–0.30). On the other hand, the lowest death rate was seen in Italy (0.01–0.02), followed by Japan (0.01–0.05). With 2 exceptions, the death rate was higher in males than in females. The 2 exceptions were Denmark during the period from 1975 to 1978 and the Netherlands. In 11 of 17 countries, the amyloidosis death rates were obtained for 2 different periods. The death rate increased in 5 countries for both sexes and in 3 countries for females. On the other hand, the death rate decreased in 4 countries for males and in 2 countries for females. The death rate was constant with the period in Sweden and was constant for white males in the United States and females in Australia. Therefore, in many countries, the amyloidosis death rate increased. The tendency was stronger in females than in males. In Japan, the death rates (per 100,000 population) in 1985 were 0.13 for males and 0.11 for females, and these values were similar to those in Canada for 1974 and

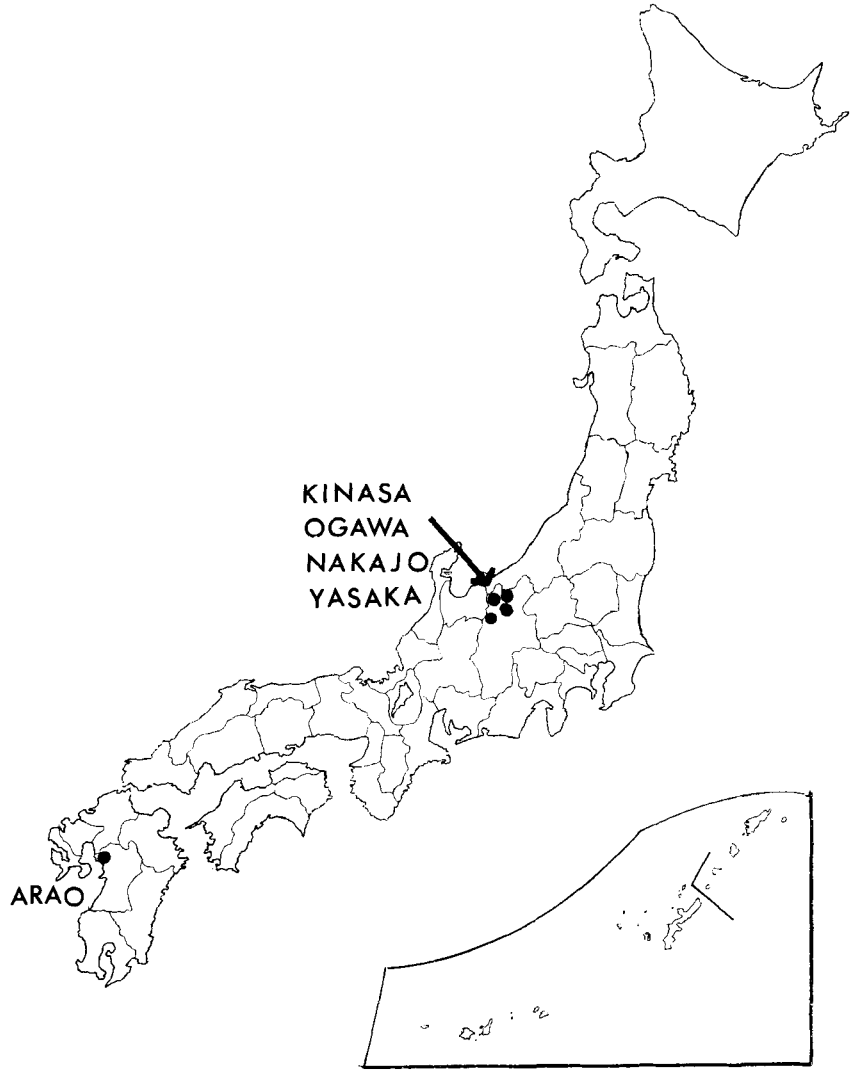

Fig. 2. Areas of higher amyloidosis death rate during 1979–1985.

1976–1977 and in the United States for whites for 1973–1978.

In the present study, the amyloidosis death rate increased year by year (Table I). The ratios of overall amyloidosis death rate during the period from 1979 to 1985 to that during the period from 1969 to 1978 were 2.6 for males and 3.3 for females (Fig. 1). The corresponding ratios were 3.2 and 5.8 for the 70–74 year age group and 3.3 and 4.3 for over 75 years of age, respectively. Therefore, incomplete ascertainment of amyloidosis was common in older people for both sexes in the earlier period. As for geographical variation, incomplete ascertainment of amyloidosis was common in several prefectures in the earlier period (Table II). From a statistical point of view, the geographical variation in the death rate was reduced in Japan during recent years. It seems that ascertainment of amyloidosis had increased overall in Japan in recent years. The increased amyloidosis death rate might be explained by the improved ascertainment of amyloidosis.

As shown in Table II, the amyloidosis death rate was highest in Kumamoto and Nagano prefectures. The second highest death rate was seen in Nagasaki and Saga prefectures, which are located in the neighborhood of Kumamoto Prefecture. FAP patients from Ogawa village (Nagano Prefecture) and Arao city (Kumamoto prefecture) had the same valine-to-methionine substitution at position 30 of transthyretin [Yoshioka et al., 1986]. In the present study, there were 68 deaths from amyloidosis in Nagano Prefecture and 59 in Kumamoto

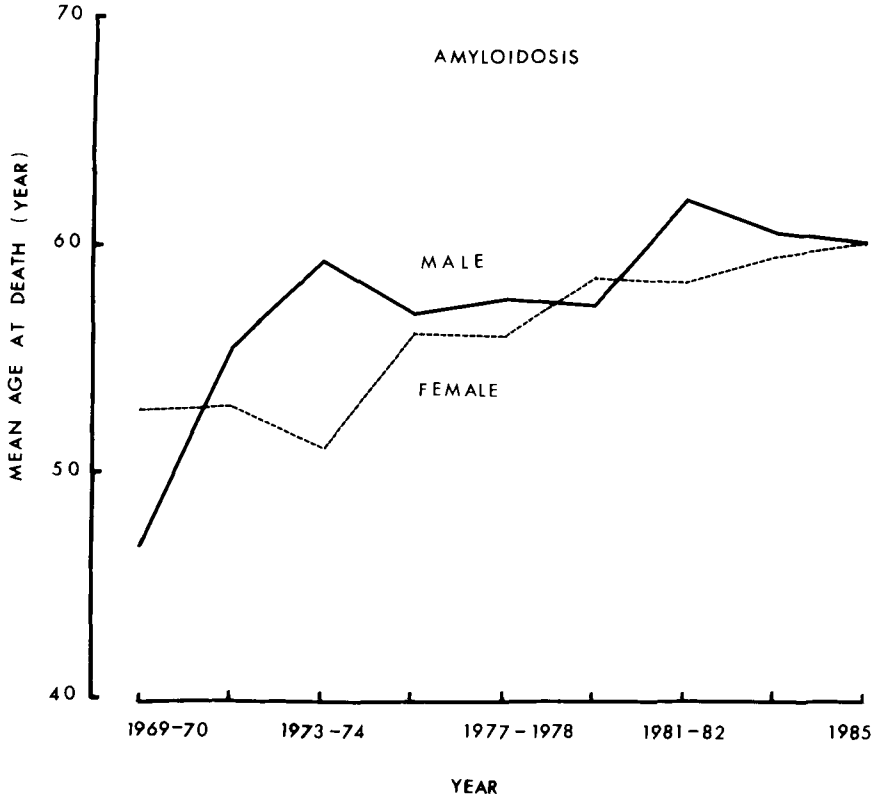

Fig. 3. Trends of mean age at death from amyloidosis by sex during 1969–1985.

Prefecture. However, it is not known whether these amyloidosis deaths were FAP or not. However, it seems that the greater part of deaths from amyloidosis are FAP related.

Recently, the prevalence rates of amyloidosis were examined in 2 prefectures during the period from 1977 to 1981 [Japan Ministry of Health and Welfare, 1983–1984]. Average annual prevalence rates of amyloidosis were 0.06 (17/27,866,000) in Hokkaido and 0.26 (16/6,228,157) in Yamagata Prefecture per 100,000 of the population for the 5 years. The ratios of the prevalence rate to the death rate of amyloidosis were 1.7 in Hokkaido and 2.6 in Yamagata Prefecture. Therefore, the prevalence rate of amyloidosis is 2 times higher than the death rate of amyloidosis.

According to Mahloudji et al. [1969], the length of life is shortened in the Andrade or Portuguese type (amyloidosis I), but life is not shortened in the Rukavina or Indiana type (amyloidosis II). The mean age at the onset of FAP (amyloidosis I) in Arao district was 33.6 years for males and 35.0 years for females [Sakota et al., 1983]. The duration of the illness was 8.8 years, and the mean age of deaths from FAP was 44.2 years in Arao district [Araki, 1986]. In the present study, the mean age at death from amyloidosis in 1969–1970 was 47 years for men and 53 years for women, and the corresponding value in 1985 was 60 years for both sexes. Accordingly, for the last 15 years, the mean age at death from amyloidosis was prolonged 13 years for boys and 7 years for girls. As compared with FAP, the mean age at death from amyloidosis was slightly higher, because deaths certified as caused by amyloidosis included not only FAP. On the other hand, Japanese life expectancy in 1969 was 69.2 years for men and 74.7 years for women, and the corresponding values in 1985 were 74.8 and 80.5 years, respectively [Japan Ministry of Health and Welfare, 1987]. Accordingly, for the last 15 years, the mean age at death from amyloidosis was 11–23 years shorter for males and 20–25 years shorter for females, compared with the national average.

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