ARTICLE

Mortality Among Persons With a History of Kawasaki Disease in Japan

The Fifth Look

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Objective: To determine whether patients with Kawasaki disease have a higher death rate than an age-matched healthy population after disease occurrence.

Study Design: From July 1, 1982, to December 31, 1992, 52 collaborating hospitals collected data on all patients with a new definite diagnosis of Kawasaki disease. Patients were followed up until December 31, 1999, or death. The expected number of deaths was calculated from Japanese vital statistics data and compared with the observed number.

Results: Of 6576 patients enrolled, 27 (19 male, 8 female) died. The standardized mortality ratio (the observed number of deaths divided by the expected number of deaths based on the vital statistics in Japan) was 1.25 (95% confidence interval, 0.84-1.85). Despite the high standardized mortality ratios during the acute disease phase, the mortality rate was not high after the acute phase for the entire group of patients. Although the standardized mortality ratio after the acute phase was 0.76 for those without cardiac sequelae, 6 male patients (no female patients) with cardiac sequelae died during this period, and the standardized mortality ratio for the male group with cardiac sequelae was 2.35 (95% confidence interval, 0.96-5.19).

Conclusions: Although it was not statistically significant, the mortality rate among male patients with cardiac sequelae due to Kawasaki disease seemed higher than that in the general population. On the other hand, mortality rates for female patients with sequelae and both male and female patients without sequelae were not elevated.

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SINCE 1991, the Kawasaki Disease Follow-up Group has been following up a cohort of persons with a history of Kawasaki disease.[1-4] The aim of this study was to determine whether the mortality among those persons is higher than in the general population. Because Kawasaki disease as a kind of vasculitis may be associated with rapidly accelerated atherosclerosis,[5-7] the history may be a risk factor of cardiovascular disease when patients become adults.

Differing from long-term follow-up data from hospitals,[8-11] our data are unbiased because the cohort includes all patients who fulfill the inclusion criteria from the nationwide survey's database. The latest follow-up ended on December 31, 1997,[4] and the current study prolonged the observation period until December 31, 1999.

RESULTS

The sex and age distribution of the cohort members at the onset of Kawasaki disease is given in **Table 1**. The distribution was similar to the epidemiologic features of Kawasaki disease in Japan.[16] On December 31, 1999, the oldest cohort member was 29 years and the youngest was 7 years. The age and sex distribution on that day is given in **Table 2**. Before that day, 27 patients had died. We could not certify whether 26 persons were still alive after January 1, 2000, and they became lost to follow-up in the current observation. Finally, the follow-up rate was 99.6% (6576-6526/6576). Of these members, 1003 (15.3%, 649 male patients and 354 female patients) were reported to nationwide surveys as having cardiac sequelae; the proportion was also reasonable in comparison with the whole group of patients with Kawasaki disease in Japan.[16]

The observed person-years were 83 162.3 for all members, 47 469.3 for male patients, and 35693.0 for female patients; therefore, the average observation periods were 12.6 years for both sexes (12.6 and 12.7 years for male and female patients, respectively).

Table 3 gives the numbers of deaths and standardized mortality ratios for the 5

PATIENTS AND METHODS

The items and methods used in this study were similar to those in the previous follow-up.[1-4] The study was reviewed by the Jichi Medical School Institutional Review Board and was exempt from review.

INCLUSION CRITERIA

In 5 nationwide surveys of Kawasaki disease in Japan, 8417 patients at 52 collaborating hospitals from July 1, 1982, through December 31, 1992, were considered for the study. From these potential cohort members, we excluded 652 patients because they did not have a definite diagnosis according to the diagnostic guidelines established by the Japan Kawasaki Disease Research Committee,[12] 384 patients with recurrent disease, 786 patients presenting on or after the 15th day of illness, and 19 non-Japanese patients. Therefore, only patients with an initial episode of a definite diagnosis of Kawasaki disease who were of Japanese nationality and who visited the hospital less than 15 days after the onset of symptoms were included in this study. A definite case means a patient with Kawasaki disease who has at least 5 of 6 major symptoms or 4 symptoms plus cardiac lesions.[12] The condition placed on the date of the first visit was intended to avoid bias caused by the inclusion of patients with late cardiac sequelae seen at large referral hospitals. Non-Japanese patients were excluded because the resident registration system for non-Japanese people is different from that for Japanese people, and the system for non-Japanese patients is not available for follow-up. Finally, we enrolled 6576 patients.

PROTOCOL

The cohort members had been followed up from the time they first came to the hospitals until December 31, 1999, or time of death if it occurred before that date. For all the members, excluding those whose deaths were known through the previous observations, we checked resident registration records or the Koseki system (permanent resident registration system)[13] in municipal offices in 2000. The resident registration system, which is administrated by a municipal government, lists residents and their Japanese addresses. The permanent resident registration lists Japanese registrants in any place in the country. It is easier to access the resident registration system than the permanent system, but a Japanese person who lives abroad is registered only in the permanent system because he or she does not have an address in Japan. Therefore, we first checked the resident registration system; if the patient was not registered in the resident registration system, we then checked the permanent system. Registration in at least 1 of the 2 systems told us that the patient was alive on or after January 1, 2000. If a patient died before December 31, 1999, the systems also provided this information. In case of death, copies of death certificates were obtained to determine the causes of deaths from local officers of the District Legal Affairs Bureaus, Ministry of Justice. Official approval by the Civil Affairs Bureau of the Ministry of Justice of the Japanese government was obtained to use these records.

STATISTICAL ANALYSIS

The duration of observation was calculated according to sex, age, and calendar year for each patient. The expected number of deaths was calculated by multiplying the observation time for each patient by the death rate calculated from Japanese vital statistics data for each group defined by sex, age, and calendar year. Standardized mortality ratios, or the ratio of the observed numbers of deaths to expected ones, were calculated by sex, phase of illness (acute disease phase within 2 months after the first visit to the hospital and after), and whether the patient experienced cardiac sequelae after the acute disease phase. In the nationwide surveys of Kawasaki disease when the follow-up started, the cardiac sequelae were defined as presence of dilation (including aneurysms), stenosis, occlusion of coronary artery and/or myocardial infarction, or valvular lesion 1 month after onset of Kawasaki disease.[14] A 95% confidence interval was calculated for each ratio based on Poisson distribution.[15] A standardized mortality ratio of which the 95% confidence interval did not include 1.0 was considered to be statistically significant.

subgroups by sex. Among all the cohort members, 27 deaths occurred (19 male deaths and 8 female deaths). The standardized mortality ratio for male patients was elevated slightly and that for female patients was similar to unity; both were not significant. The mortality was high during the acute phase of Kawasaki disease but not high after the acute phase. However, the elevated mortality rate after the acute phase was observed only among those with cardiac sequelae, especially for male patients. Six cases with cardiac sequelae, all of whom were male patients, died after the acute phase, and the standardized mortality ratio was 2.35, which almost reached statistical significance.

Detailed information of the fatal cases is given in **Table 4**. Of the 8 patients who died during the acute phase, 7 deaths were owing to Kawasaki disease and 1 was owing to drowning in the bath at home. After the acute phase, 19 patients died. Two patients died of coronary artery insufficiency owing to Kawasaki disease; 1 death was 11 months after the onset of Kawasaki disease, and 1 death was 6 years later. Kawasaki disease was not mentioned on the death certificates of the other 2 patients, but the disease was suspected to be related to the deaths. Because postmortem examinations were not conducted for the 2 patients according to the death certificates, no more detailed information was available. Because of the lack of nec-

Table 1. Age and Sex Distribution at Recruitment*

Age, y	Male Patients	Female Patients	Total
0	1174 (31.2)	881 (31.3)	**2055** (31.2)
1	1061 (28.2)	757 (26.9)	**1818** (27.6)
2	593 (15.8)	455 (16.2)	**1048** (15.9)
3	354 (9.4)	300 (10.7)	**654** (9.9)
4	260 (6.9)	192 (6.8)	**452** (6.9)
5-9	310 (8.2)	222 (7.9)	**532** (8.1)
≥10	12 (0.3)	5 (0.2)	**17** (0.3)
Total	**3764 (100)**	**2812 (100)**	**6576 (100)**

*Data are presented as number (percentage). Percentages may not total because of rounding.

Table 2. Age Distribution at the End of Follow-up (December 31, 1999)*

Age, y	Male Patients	Female Patients	Total
0-4	0	0	0
5-9	339 (9.0)	231 (8.2)	**570** (8.7)
10-14	1507 (40.0)	1117 (39.7)	**2624** (39.9)
15-19	1654 (43.9)	1277 (45.4)	**2931** (44.6)
20-24	222 (5.9)	159 (5.7)	**381** (5.8)
25-59	10 (0.3)	7 (0.2)	**17** (0.3)
Died	19 (0.5)	8 (0.3)	**27** (0.4)
Not followed up	13 (0.3)	13 (0.5)	**26** (0.4)
Total	**3764 (100)**	**2812 (100)**	**6576 (100)**

*Data are presented as number (percentage). Percentages may not total because of rounding.

Table 3. Numbers of Observed and Expected Deaths and Standardized Mortality Ratios*

Variable	No. of Deaths		Ratio of Observed to Expected Deaths (95% Confidence Interval)
	Observed	Expected	
Entire study period			
All patients	27	21.6	1.25 (0.84-1.85)
Male	19	14.4	1.32 (0.82-2.10)
Female	8	7.2	1.12 (0.52-2.30)
During acute phase			
All patients	8	1.0	8.22 (3.82-16.9)
Male	6	0.6	9.84 (4.00-22.6)
Female	2	0.4	5.50 (0.95-22.2)
After acute phase			
All patients	19	20.6	0.92 (0.57-1.47)
Male	13	13.8	0.94 (0.52-1.66)
Female	6	6.8	0.88 (0.36-2.03)
After acute phase (with cardiac sequelae)			
All patients	6	3.5	1.72 (0.70-3.95)
Male	6	2.6	2.35 (0.96-5.39)
Female	0	0.9	0.00
After acute phase (without cardiac sequelae)			
All patients	13	17.1	0.76 (0.42-1.34)
Male	7	11.2	0.62 (0.27-1.35)
Female	6	5.9	1.02 (0.42-2.35)

*Acute phase of the disease defined as the first 2 months of the observation.

ropsy, it was not certain whether the patient who died suddenly during swimming in a swimming pool had had a myocardial infarction or whether he simply drowned.

COMMENT

This is the fifth look at the cohort consisting of all patients with Kawasaki disease who were eligible for inclusion. The current follow-up data show that persons with cardiac sequelae owing to Kawasaki disease were somewhat more likely to die than the general population. This phenomenon was only true for male patients; the mortality rate for male patients with the sequelae was 2.35 times as high as in the general population and was not statistically significant.

The aim of the study was to determine whether the mortality rate among patients with a history of Kawasaki

Table 4. Causes of Deaths for the 27 Fatal Cases*

Disease Phase	Causes of Death	Period Between Kawasaki Disease and Death
During the acute phase		
Kawasaki disease (n = 7)	Mitral insufficiency	18 d
	Mitral insufficiency	28 d
	Coronary artery aneurysm	13 d
	Myocardial infarction	14 d
	Myocarditis	4 d
	Heart failure	51 d
	Acute encephalopathy	22 d
Other (n = 1)	Drowning (bath)	59 d
After the acute phase		
Kawasaki disease (n = 2)	Coronary artery insufficiency	11 mo
	Coronary artery insufficiency	6 y
Kawasaki disease suspected (n = 2)	Sudden death during swimming	6 y
	Myocardial infarction	13 y
Congenital heart diseases (n = 4)	Aortic coarctation	21 mo
	Endocardial cushion defect	22 mo
	Pulmonary atresia	8 y
	Tetralogy of Fallot	10 y
Neoplasms (n = 3)	Acute lymphatic leukemia	3 mo
	Malignant reticuloma	5 mo
	Osteosarcoma	9 y
Other disease (n = 3)	Pneumonia	3 mo
	Sudden infant death syndrome	4mo
	Pneumonia due to flu	7 y
Injuries (n = 5)	Unintentional injury (falling in home)	29 mo
	Unintentional injury (hanging with a curtain at home)	4 y
	Motor vehicle crash	4 y
	Suicide	13 y
	Homicide	9 y

*The causes of deaths are from the death certificates. The acute phase of the disease was defined as the first 2 months of the observation.

disease was higher than that of general population. Several hypotheses should be considered regarding this study question. One concerns the cardiac sequelae owing to the disease, which developed in 10% to 15% of the patients when the observation started. Indeed, 1003 patients (15.3%) in this cohort had sequelae. This issue is revealed by the current study. Six male patients with cardiac sequelae died after the acute phase, whereas the expected number of deaths for this group was 2.6 (Table 3). This means that there were 3.4 (6 – 2.6) excess deaths. Fortunately, no death was observed during the most recent 2-year period (1998-1999) (the current observation). However, we should observe the cohort longer to obtain definite conclusions.

The mortality rate for female patients with cardiac sequelae was not elevated. Kawasaki disease is more prevalent among males than females, and the proportion of patients with cardiac sequelae is higher in males.[15] Therefore, the expected number of death was small among female patients with cardiac sequelae, and the high mortality rate was observed only for male patients in this study. Using Poisson distribution with the expected number of 0.934 for female patients after the acute phase, the prob-

What This Study Adds

Kawasaki disease is now the leading cause of acquired heart disease in childhood, but its long-time prognosis is still unknown. In addition, following up all patients with the disease, not just patients with cardiac sequelae caused by the disease, is important to reveal the effects of the vasculitis of the disease to the cardiovascular system, especially for atherosclerosis. Such a cohort has been followed up in Japan. This study prolonged the follow-up period (average follow-up, 12.6 years). In contrast to the high mortality rate during the acute disease phase, the mortality rate was not elevated for those without cardiac sequelae after the acute phase. On the other hand, high but not significant mortality was observed for male patients with cardiac sequelae after the acute phase of the disease.

ability that no patient died is 0.393. Thus, no fatal case among this group might occur by chance. However, longer observation is required to reveal whether females with cardiac sequelae have a high mortality rate.

Another issue is ischemic heart disease and cerebrovascular disease owing to atherosclerosis induced by the systemic vasculitis in childhood. Some pathologic observations reveals that atherosclerosis progressed in autopsy cases with a history of Kawasaki disease more than those with similar age but without the history.[5,17,18] Unfortunately, because the cohort was established in 1991, many of the members were teens when the current observation was conducted (Table 2). The oldest person in the cohort was 29 years old on the last day of observation. Thus, the risk of cardiovascular and cerebrovascular diseases was still low. On the other hand, a recent study[19] showed that coronary endothelial function was impaired from Kawasaki disease onset after 1 to 12 years, even in cases with regression of coronary artery aneurysms. If so, the mortality is expected to become close to that of persons without a history of Kawasaki disease according to the passage of time. Further long-term observation is required to discuss the issue.

The final issue is intravenous γ-globulin therapy and the immune system. Unusual immune system response of the disease is well known.[20,21] In addition, many patients with Kawasaki disease are treated with γ-globulin.[22] Large amounts of external immunoglobulin for children may affect the immune system, and the incidence of immunologic disease may increase after years. Fortunately, such diseases or abnormalities are not reported to date. Two persons have died of malignant neoplasm of the lymphatic or hematopoietic tissue, but the mortality was not significantly high.[3] Further observation is necessary regarding this issue.

Cause-specific mortality rates among the cohort are of interest. We have shown them in the third observation.[3] However, precision was low because the expected numbers of deaths were so small owing to the size of the cohort, and there were wide 95% confidence intervals of the standardized mortality rates. In the current study, we refrained from observing these patients because the observation period after the fourth observation was only 2 years. However, continuing to observe this cohort will provide such data in the near future. A recent study[23] showed that those with a history of Kawasaki disease had more cardiovascular risk factors, such as obesity, hypertension, and hypercholesteremia, than those without a history. Control of these risk factors is essential for the health management of those with a history of the disease.

In conclusion, although the findings are not significant, the current epidemiologic observation showed that mortality among persons with cardiac sequelae owing to Kawasaki disease was high among male patients.

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