

# Results of the Nationwide Epidemiologic Survey of Kawasaki Disease in 1995 and 1996 in Japan

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**ABSTRACT.** *Objective.* The objective of the study is to describe recent epidemiologic patterns of Kawasaki disease based on information included in patient records that had been obtained through a nationwide hospital survey in Japan.

*Methods.* A questionnaire and diagnostic criteria for Kawasaki disease that had been approved by the Kawasaki Disease Research Committee were sent to all pediatric departments of hospitals (2638 hospitals) with a bed capacity of at least 100. The subjects all were new patients who were treated during a 2-year period from 1995 to 1996.

*Results.* A total of 12 531 children contracted the disease during the observation period. The incidence was 102.6 for 1995 and 108.0 for 1996 per 100 000 children younger than age 5 years. The male:female ratio was 1.37. The age distribution pattern showed a peak near 6 months of age. Geographic variations in the incidence suggested the existence of local outbreaks. Cardiac sequelae were seen in 12% of the patients.

*Conclusion.* More than 6000 patients suffered from Kawasaki disease each year, and its annual incidence is increasing steadily. The probable existence of local outbreaks is worthy of note. Other epidemiologic patterns were unchanged from previous years. *Pediatrics* 1998; 102(6). URL: <http://www.pediatrics.org/cgi/content/full/102/6/e65>; *Kawasaki disease, epidemiology, incidence survey, Japan.*

ABBREVIATION. IVGG, intravenous gamma globulin.

Fourteen nationwide epidemiologic surveys have been conducted in alternate years since 1970. The results of the last survey, covering the past 2 years (1995 and 1996) have just been tabulated. This article summarizes the recent trend in the epidemiologic presentation of Kawasaki disease in Japan, based on the tabulated results obtained from this survey.

## METHODS

The 14th Nationwide Epidemiologic Survey on Kawasaki Disease basically followed the same protocol as the 13 previous surveys. The details are described elsewhere.<sup>1-6</sup> The questionnaire and diagnostic guidelines (4th edition, Japan Kawasaki Disease Research Committee; 1984) were sent in January 1997 to 2627

Japanese hospitals, ie, those with a bed capacity of 100 or more. Additional inquiries were sent twice more (in March and May 1997) to nonresponding hospitals. Included in the questionnaire were the patient's name, address, gender, date of birth, date of first hospital visit, diagnostic criteria, intravenous gamma globulin (IVGG) treatment and dosages, primary onset or recurrence, blood platelet count, familial incidences, cardiac sequelae, and fatalities.

The diagnostic criteria for typical Kawasaki disease in this series were having at least five of the following six principal symptoms:

1. fever persisting for 5 or more days,
2. changes to the peripheral extremities,
3. polymorphous exanthema,
4. bilateral conjunctival congestion,
5. changes to the lips and oral cavity, or
6. acute nonpurulent cervical lymphadenopathy.

Atypical cases are defined as those with at least four of the symptoms listed above when a coronary involvement was detected by two-dimensional echocardiography or coronary angiography. A patient was suspected to have Kawasaki disease when the clinical presentation was not consistent with the criteria listed above.

The incidence was based on data obtained from the 1995 National Census of Japan. Differences in response rates were adjusted in the comparison of the geographic distribution of incidences among 47 prefectures.

## RESULTS

Of the 2627 hospitals to which questionnaires were sent, 1777, or 67.6%, responded after two additional inquiries; of those, 1059 (59.6% of the responding hospitals) reported one or more patients with Kawasaki disease.

The number of patients reported in this survey by gender, year of onset, age, and diagnosis is shown in Table 1. The total was 12 531 (7239 males, 5292 females; male:female ratio = 1.37); and 6107 were diagnosed in 1995 and 6424 in 1996. The incidence was 102.6 for 1995 and 108.0 for 1996, both per 100 000 children younger than 5 years old. Of the total, 6777, or 54.1%, were younger than 2 years of age. According to the diagnostic criteria, 84.8% were typical, 3.5% atypical, and 11.7% were suspected of having Kawasaki disease.

Yearly distribution of the incidence (per 100 000 children younger than 5 years old), based on the results of the previous 13 nationwide surveys, is compared in Fig 1. Since 1987, the incidence rose steadily for both males and females, although unusual outbreaks such as those that had occurred in 1979, 1982, and 1986 were not seen. As noted, the incidence in 1996 was 108.0, the third highest (the others being 196.1 in 1982 and 176.8 in 1986).

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**TABLE 1.** Number of Patients With Kawasaki Disease in Japan by Gender, Year of Onset, Age, and Diagnosis (1995 and 1996)

	Total	Male	Female
Total	12 531	7239	5292
Year of onset			
1995	6107	3548	2559
1996	6424	3691	2733
Age at onset			
<6 mo	1402	822	580
6 mo	2207	1326	881
1 y	3168	1864	1304
2 y	4385	2439	1946
5 y	1277	734	543
10 y	77	46	31
Unknown	15	8	7
Diagnosis			
Typical	10 628	6166	4462
Atypical	438	260	178
Suspected	1465	813	652

The monthly distribution of the number of patients is shown in Fig 2. Although the seasonal variation was not clear, the number of patients was lowest in the fall, especially in October, for both years.

The average annual incidence by age is shown in Fig 3. The curves for males and females have one peak between 3 and 5 months to between 9 and 11 months after birth, with a steep increase on the left side and a gradual decrease as patients become older. Children between 6 months and 2 years of age mostly accounted for the male:female difference.

The geographic distribution of the incidences for 47 prefectures in 1995 and 1996, which was adjusted for the differences in response rates among the prefectures, is illustrated in Fig 4. Areas of high incidence were found in Tokyo and the surrounding prefectures in 1995. These areas of high incidence extended to various prefectures, primarily in the western part of the country, in 1996. The differences in incidence among prefectures were 5.3-fold in 1995 and 3.3-fold in 1996, on the basis of adjusted incidence rates. The incidence in Okinawa prefecture, which is located to the far southwest of the four major islands, was the lowest among all prefectures, in both 1995 and 1996.

Of total patients reported, 10 were fatal (fatality rate, 0.08%). The fatality rate was higher in those younger than 1 year (0.16%) compared with those  $\geq 1$  year (0.05%).

The percentages of patients with incidences of Kawasaki disease among siblings and those with recurrences are shown in Table 2. The former, at 0.9%, was higher for females and older patients. The latter, at 3.3%, was higher in males and older patients.

The number and percentages of patients with cardiac sequelae according to gender and age are shown in Table 3. Of the total reported, 12.1% developed cardiac sequelae; its incidence was higher in males, in those younger than 6 months of age, and in patients  $\geq 10$  years of age. The percentage of patients who developed giant coronary aneurysms was 0.8%, which was higher in patients younger than 6 months and those  $\geq 5$  years. By definition, the incidences of cardiac sequelae and giant aneurysms were higher in atypical patients.

## DISCUSSION

Since 1970, we have conducted nationwide surveys every 2 years on the incidence of Kawasaki disease. All hospitals that have a bed capacity of at least 100 and a pediatric department have been included. Recently, a compilation of the data for the 14th Nationwide Epidemiologic Survey has been completed. The total number of patients included in the surveys is 140 837.<sup>4,6</sup> All patient data have been entered into a computer database.

Because the hospitals from which the data were collected were limited to those with bed capacities of at least 100, all patients suffering from Kawasaki disease in Japan clearly have not been included. However, because of persistent fever, >80% of those with this disease who originally sought treatment at small hospitals or private clinics have been referred to hospitals with a bed capacity of at least 100.<sup>7</sup>

In striving to maintain the past questionnaire retrieval rate, a 67.6% rate was achieved, which is comparable with rates for the past surveys.<sup>6</sup> Although not all patients are included in the survey, we believe that this is an epidemiologic survey with a level of comprehensiveness that is unknown in other countries.

From the results of the present survey, several important facts that should not be handled casually have been revealed. They are discussed briefly below.

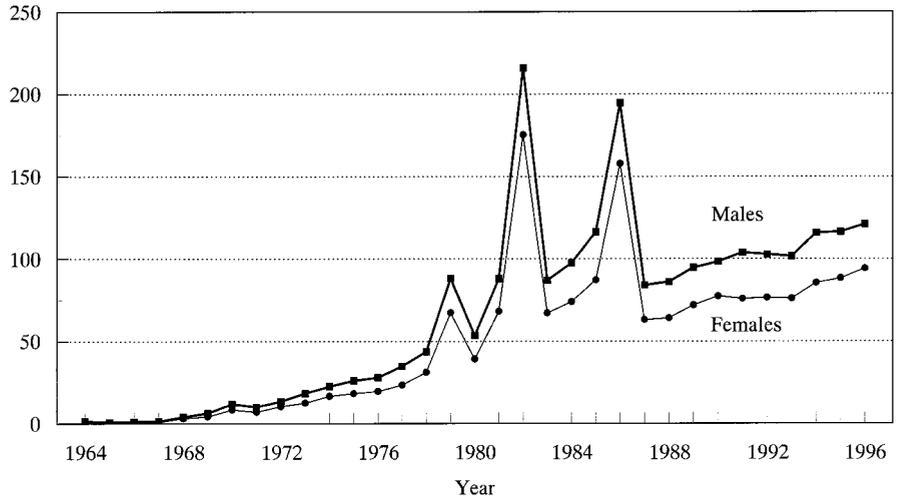
Since the third notable epidemic of 1986, the number of patients has been steadily rising in spite of a decline in the number of children younger than 5 years of age because of a decrease in the birth rate in Japan.<sup>6,8</sup> There were  $\sim 5000$  patients after 1987, which has exceeded 6000 since 1994. The number of patients per 100 000 children younger than 5 years of age has passed 100. It is anticipated that this tendency for the number of patients with Kawasaki disease to increase will continue. It is necessary to organize an information collection system so that the incidence of this disease in this country can be monitored adequately.

Since the three outbreaks of 1979, 1982, and 1986, no abnormal increase in incidence at the national level or any other sign of an epidemic has been noted.<sup>4,6,9,10</sup> However, an evident increase in incidence was seen in central Japan, with Tokyo at its center, in 1995, and in a wide area in western Japan in 1996. The differences among prefectures were adjusted for the variations in response rates from these prefectures; therefore, it is believed that a bias attributable to reporting was avoided in this analysis.

The prefectural difference in incidence rose to 5.3-fold in 1995 and 3.3-fold in 1996, indicating that there were regional epidemics then.

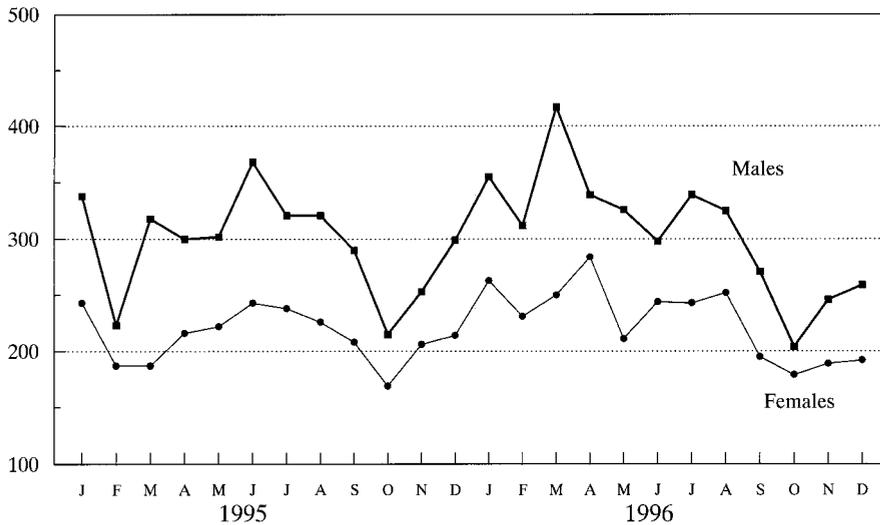
The reason for the wide gender difference seen in those between 6 months and 2 years of age cannot be explained by the difference in exposure between males and females, because the behavioral pattern, housing environment, and dietary habits are generally similar for children in that age group. However, it may be attributable to a difference in genetic or other host factors.

per 100,000 children of age <5 years



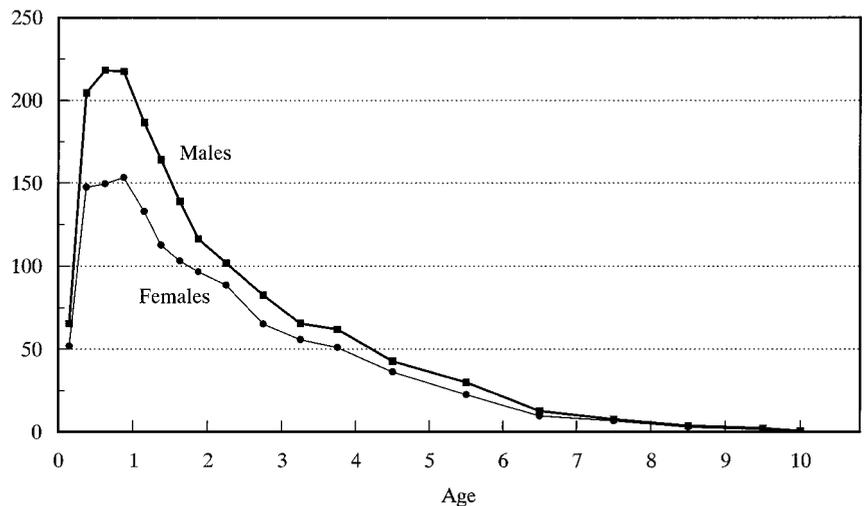
**Fig 1.** Incidence rates of Kawasaki disease in Japan by year and gender.

No. of patients



**Fig 2.** Number of patients with Kawasaki disease in Japan by month and gender (1995 and 1996).

per 100,000 children



**Fig 3.** Age-specific incidence rate of Kawasaki disease in Japan by gender (average of 1995 and 1996).

The proportion of fatalities among the patients reported was >1% before 1975 and >0.3% before 1984. This rate decreased to <0.1% after the introduction of IVGG treatment.<sup>6,11,12</sup>

The proportion of patients with a family history of Kawasaki disease (0.9% in this study) was almost the same as those in the previous surveys. We calculated the incidence of family history as a second case of

1995

1996

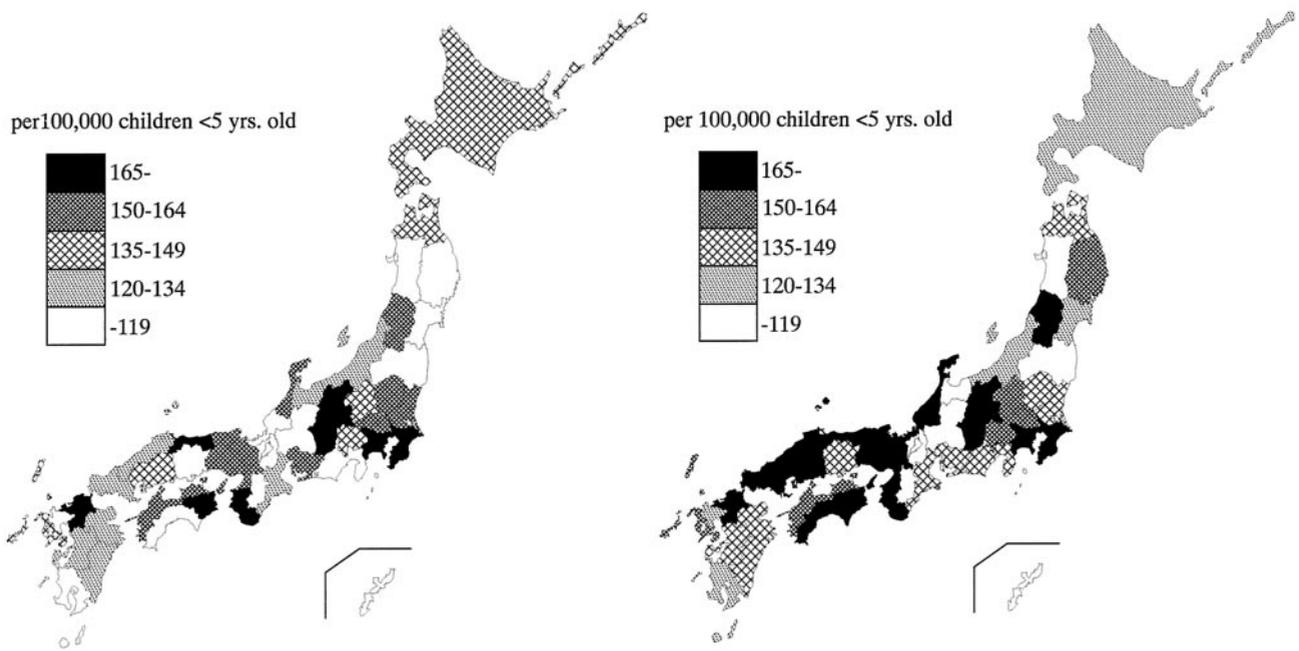


Fig 4. Geographic differences in incidence rate of Kawasaki disease in Japan by prefecture, adjusted for response rate.

**TABLE 2.** Number of Patients With Kawasaki Disease With Family History and Recurrence by Age and Gender in Japan (1995 and 1996)

	Total	With Family History		Recurrence	
		No.	%	No.	%
Total	12 531	115	0.9	413	3.3
Sex					
Male	7239	57	0.8	256	3.5
Female	5292	58	1.1	157	3.0
Age					
<6 mo	1402	7	0.5	2	0.1
6 mo	2207	17	0.8	19	0.9
1 y	3168	27	0.9	74	2.3
2 y	4385	41	0.9	214	4.9
5 y	1277	23	1.8	95	7.4
10 y	77	—	—	9	11.7
Unknown	15	—	—	—	—

Kawasaki disease in siblings 1 year after the onset in the epidemic year of 1982. It was 2%, which was 10 times higher than the expected rate for the general population.<sup>13</sup>

Recurrence was 3.3% for the total patient population reported in this study. In 1982, after 4500 patients had been followed for >3 years, it was found that 5.2 per 1000 person-years experienced recurrence within 2 years of the first episode.<sup>14</sup> A case-control study on factors associated with recurrence in patients reported in 1991 and 1992 disclosed that the risk of recurrence increased in those who were treated with IVGG.<sup>15</sup> Those who received a high dose of IVGG should be followed carefully.

The high incidence of cardiac sequelae in those younger than 1 year of age and of male gender agrees with the results of earlier surveys. The incidence of cardiac sequelae shows a generally linear

**TABLE 3.** Number of Patients With Kawasaki Disease With Cardiac Sequelae by Gender, Year of Onset, Age, and Diagnosis in Japan (1995 and 1996)

	Total	With Cardiac Sequelae	%	With Giant Aneurysms	%
Total	12 531	1510	12.1	100	0.8
Sex					
Male	7239	1031	14.2	80	1.1
Female	5292	479	9.1	20	0.4
Year of onset					
1995	6107	732	12.0	42	0.7
1996	6424	778	12.1	58	0.9
Age					
<6 mo	1402	259	18.5	23	1.6
6 mo	2207	248	11.2	11	0.5
1 y	3168	345	10.9	13	0.4
2 y	4385	451	10.3	29	0.7
5 y	1277	187	14.6	21	1.6
10 y	77	17	22.1	3	3.9
Unknown	15	3	20.0	—	—
Diagnosis					
Typical	10 628	1271	12.0	91	0.9
Atypical	438	189	43.2	8	1.8
Suspected	1465	50	3.4	1	0.1

reduction, possibly attributable to the increase in the percentage of patients treated with IVGG and an increase in daily dosage.<sup>16–18</sup>

Nationwide surveys have been conducted in Japan for more than 25 years. The more recent surveys were fortified with additional information. For example, information was sought on the white blood cell count and c-reactive protein in the 13th survey (1993–1994). An analysis of the results of these laboratory examinations has been published previously.<sup>19,20</sup>

Information on platelet count and serum albumin also was obtained in the 14th survey (1995–1996). Analyses are underway of these additional data. In

the 15th survey (between 1997 and 1998), which will be conducted in January 1999, other information obtained from clinical examinations will be included.

### CONCLUSION

The 14th Nationwide Epidemiologic Survey of Kawasaki Disease in Japan revealed that >6000 patients suffered from Kawasaki disease each year, with the annual incidence per 100 000 children younger than 5 years of age 102.6 in 1995 and 108.0 in 1996. These data indicate that there has been a steady increase in the number of cases. The probable presence of local outbreaks is worthy of note.

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DOI: 10.1542/peds.102.6.e65

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