ORIGINAL CONTRIBUTION

Update of the Epidemiology of Kawasaki Disease in Japan - From the Results of 1993-94 Nationwide Survey-

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Objective. The objective of this article is to describe the epidemiologic pictures of Kawasaki disease (KD) in Japan during the 2-year period of 1993 and 1994 based on the data obtained by the thirteenth nationwide epidemiologic survey of KD which was conducted by the Japan Kawasaki Disease Research Committee.

Methods. A survey form and diagnostic criteria of KD were sent to all hospital pediatric departments (2,640) throughout Japan with 100 or more beds. The patients to be reported in this survey were all the incident KD cases who satisfied the diagnostic criteria.

Results. (1) A total of 1,730 (65.5%) hospitals responded, reporting 11,458 (5,389 in 1993 and 6,069 in 1994; 6,729 males and 4,729 females; male/female ratio = 1.42) with an incidence rate of 95.1 per 100,000 children of age <5 years. (2) The monthly number of patients was higher in winter and summer, although the monthly difference was not marked. (3) Age specific incidence rates showed a uni-modal peak at one year of age. (4) The proportion of patients with family history of KD in sibling was 1%. (5) The proportion of recurrent patients was 3%. (6) The proportion of patients with cardiac sequelae in one month after disease onset was 13%. (7) Number of fatal patients reported was 9, which conforms to 0.08% of total patients.

The results of former surveys have been published elsewhere. In addition to the items included in the previous surveys, records of two basic clinical examinations (highest values of white blood cell count and C-reactive protein (CRP) level during the acute stage) were newly included in the questionnaire form.

METHODS

We sent a questionnaire form and diagnostic guidelines for KD with color printed photos of patients with typical clinical symptoms to all pediatric departments of hospitals with 100 or more beds throughout Japan in January 1995, and requested to report all the patients with KD who were diagnosed during the two-year period from January 1993 through December 1994 and satisfied the diagnostic guidelines. The questions on the survey form were date of diagnosis, date of birth, sex, address, days after the onset of illness at hospital visit, information about recurrence, sibling KD history, heart sequelae, death, type of treatment, white blood cell count and CRP level.

The diagnostic criteria in this series for typical cases were defined as those with at least five of the six principal symptoms, atypical cases as those with at least four, when a coronary involvement was detected by two-dimensional echocardiography or coronary angiography, and suspected cases as those whom the physician suspected as having KD even if the clinical symptoms did not satisfy the criteria.

The cardiac sequelae were defined as “presence of dilatation (including aneurysm), stenosis, occlusion of coronary artery, and/or myocardial infarction, or valvular lesion 1 month after

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RESULTS

Of 2,640 pediatric departments of the hospitals at survey 1,730 or 65.5% responded, and among them 1,063 hospitals or 61.4% reported KD patients. The total number of patients reported in this survey was 11,458 (male 6,729 and female 4,729; male/female ratio=1.42). Average annual incidence rate was 95.1 per 100,000 children of age 0-4 years (male 108.8 and female 80.7; male/female ratio=1.35).

The numbers of patients were 5,389 in 1993 and 6,069 in 1994. The age distribution of the reported patients showed that 6,258 patients or 54.6% were <2 years old and 10,176 or 88.8% were <5 years old. According to the diagnostic criteria, 84.3% were typical, 4.0% were atypical and 11.6% were suspected (Table 1).

The yearly age-specific incidence rates by sex for the average of 1993 and 1994 were shown in Figure 1. The incidence curves were uni-modal with a peak at 3-5 months of age. (rates at peak age in the average of 1993 and 1994: males 210.1 per 100,000 children, females 151.4; male/female ratio=1.39) (Figure 1).

The geographical differences in the incidence rates among prefectures based on the estimated number of patients when the response rate of each prefecture was adjusted to 100% was observed in Figure 2. Prefectures with high incidence rate were aggregated in the Tokyo metropolitan area and surrounding prefectures in the central Japan. The incidence rates were lower in the northern part of Japan.

The number of patients by month for the two-year period of 1993 and 1994 showed increases in winter (January) and decrease in fall (October) in the typical patients. However, the seasonal differences were not clear in suspected and atypical patients (Figure 3).

Figure 4 shows the distribution of white blood cell count according to the diagnostic criteria. The peak of the white blood cell count was at 12000-14000/µl (17.1%) followed by at 14000-16000/µl (16.9%) in the typical cases. Of all the patients with white blood cell count examination, 69.8% was within the range of 10,000-20,000/µl. Although the distribution of the suspected patients shifted to the left, that of the atypical patients was almost the same as that of typical patients.

Figure 5 is the same observation on the distribution of CRP level. The peak of the distribution is at 5.0-9.0mg/dl among typical (31.2%) and atypical (34.1%). The distribution for suspected patients shifted to the left as seen in white blood cell count. However, the peak was at the same level as the other two groups.

Of total patients reported, 2.9% was recurrent patients including 0.2% with multiple recurrences of twice or more. Both increased with the increase of age up to 5 years old. The proportion of multiple recurrence corresponded to 6.9% of those with recurrence (Figure 6).

The number of fatal patients during the 2 year-period was 13 (0.10%). The case fatality rate was 4 times high in male(0.16%) as in female (0.04%) and 3 times high in age <1 year(0.21%) as in 1 year or more(0.07%) (Table 2).

The proportion of patients with cardiac sequelae was 12.8%. That in male (15.0%) was higher than that in female(9.6%). The most popular type of cardiac sequelae was dilatation.

| Table 1. Number of patients by sex, year of onset, age and diagnosis |
|---------------------------------------------------------------|
|                  | Total | Male | Female |
|------|------|------|-------|
| Year of onset  |
| 1993 | 5,389| 3,155| 2,234 |
| 1994 | 6,069| 3,574| 2,495 |
| Age   |
| <6m  | 1,400| 813  | 587   |
| 6m-  | 2,012| 1,237| 775   |
| 1y-  | 2,846| 1,688| 1,158 |
| 2y-  | 3,918| 2,265| 1,653 |
| 5y-  | 1,189| 872  | 517   |
| 10y- | 69   | 37   | 32    |
| Unknown | 24  | 17   | 7     |
| Diagnosis |
| Typical   | 9,661| 5,703| 3,958 |
| Atypical  | 463  | 277  | 186   |
| Suspected | 1,334| 749  | 585   |
(11.31%). The giant aneurysm was seen in 1.04% (Figure 7).

The proportion of patients treated with intra-venous $\gamma$-globulin (IVGG) was 84.1%. It was higher in younger age of <6 months (87.8%) and lower in age 5-9 years (79.6%) and 10 years and over (59.4%). The proportion was higher in typical patients (89.2%) and lower in suspected patients (50.9%) (Table 3).

The distribution of total dose of IVGG administration shown in Figure 8, indicated that those administered 1000mg ($\leq$100mg included)/kg shared 31.7% of all the patients treated with IVGG followed by 2000 mg/kg (20.5%), 1200mg/kg (17.4%) and 1600mg/kg (8.9%). The distribution of the day of illness starting IVGG treatment was a monomodal curve with a peak at 5th day of illness (28.7%) followed by 6th day (19.5%) and 4th day (18.2%). Proportion of patients treated at the 8th day of illness or later among those treated with

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**Figure 1.** Age specific incidence rate by sex, Average of 1993 and 1994

**Figure 2.** Incidence rate by prefecture, Average of 1993 and 1994

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* Based on estimated number of patients when the response rate of each prefecture was adjusted to 100%
Figure 3. Monthly number of patients according to the diagnostic criteria

Figure 4. Distribution of white blood cell count according to the diagnostic criteria
Figure 5. Distribution of CRP level according to the diagnostic criteria

Figure 6. Proportion of patients with single and multiple recurrence by age
Table 2. Number and percent of fatal patients by sex and age

|       | Total  | Fatal | %  |
|-------|--------|-------|----|
| Total | 11,458 | 13    | 0.10 |
| Sex   |        |       |     |
| Male  | 6,729  | 11    | 0.16 |
| Female| 4,729  | 2     | 0.04 |
| Age   |        |       |     |
| <1m   | 3,412  | 7     | 0.21 |
| 12-23m| 2,846  | 2     | 0.07 |
| 2y-   | 5,716  | 4     | 0.07 |
| Unknown| 24    | -     | -   |

Figure 7. Percent of patients with coronary sequelae by type of lesion
### Table 3. Number of patients treated with IVGG by sex, year of onset, age and diagnosis

| Sex       | Total | With IVGG | %    |
|-----------|-------|-----------|------|
| Male      | 6,729 | 5,701     | 84.7 |
| Female    | 4,729 | 3,938     | 83.3 |

| Year of onset | Total | With IVGG | %    |
|---------------|-------|-----------|------|
| 1993          | 5,389 | 4,556     | 84.5 |
| 1994          | 6,069 | 5,083     | 83.8 |

| Age | Total | With IVGG | %    |
|-----|-------|-----------|------|
| <6m | 1,400 | 1,229     | 87.8 |
| 6m- | 2,012 | 1,696     | 84.3 |
| 1y- | 2,846 | 2,401     | 84.4 |
| 2y- | 3,918 | 3,312     | 84.5 |
| 5y- | 1,189 | 946       | 79.6 |
| 10y-| 69    | 41        | 59.4 |
| Unknown | 24    | 14        | 58.4 |

| Diagnosis | Total | With IVGG | %    |
|-----------|-------|-----------|------|
| Typical   | 9,661 | 8,613     | 89.2 |
| Atypical  | 463   | 347       | 74.9 |
| Suspected | 1,334 | 679       | 50.9 |

*Analysis of 9,639 patients with IVGG treatment
Each category includes < ± 100mg/kg

**Figure 8.** Distribution of total dose of IVGG administration
IVGG was 10.9% (Figure 9).

**DISCUSSION**

Total number of patients including those reported by the end of 1992 (116,848 patients) was amounted to 128,306 patients as of the end of 1994. The objective of this report is to outline and discuss the results of the latest survey (the 13th survey for the patients diagnosed in 1993 and 1994).

The nationwide surveys on Kawasaki disease with a common diagnostic criteria with a slight modification have been conducted every two years since 1970. The facilities that participated in the surveys were limited to either hospitals with bed capacities of 100 or more and having pediatric departments or pediatric hospitals with bed capacities of less than 100. Therefore, those patients who were treated only at the clinics were not included in these surveys. However, the majority of patients with Kawasaki disease suffer from sustained fever for 5 days or more, and most of those who visit clinics first are referred to a hospital with a bed capacity of 100 or more. We believe that more than 90% of the patients with Kawasaki disease are being treated at those facilities that participated in these surveys.

The response rate of the facilities that were requested to participate in the present 13th nationwide survey was 65.5%, which approximates earlier response rates [68.9% for the 12th survey (1992 to 1993), 66.6% for the 11th (1990 to 1991), and 63.9% for the 10th (1988 to 1989)]. Although we cannot escape the bias due to the exclusion of patients who were treated at facilities that failed to respond to our request, it is practically impossible to obtain a response rate that exceeds those given above. This is the only nationwide survey using the uniform diagnostic criteria and we believe that the resultant data are the most reliable among those available in this country at the moment. The response rates vary among prefectures and other municipal districts. Therefore only when regional differences in the morbidity specific to each district were compared, the estimated number of patients was used based on assumption that the response rate from all prefectural and other municipal districts to be 100%.

The reported annual incidence has remained generally the same since 1987 (5,500 ± 200 per year); but in 1994 it increased by approximately 10%, exceeding 6,000. Twice in the past we experienced large-scale nationwide epidemics involving more than 10,000 patients (15,519 in 1982 and 12,847 in 1986) but no such epidemics have been witnessed in the last 8 years.

The male/female ratio among patients with Kawasaki dis-
ease is 1.35, which has been unchanged throughout the past surveys. It should be noted, however, that in 1982 and 1986 when epidemics swept the nation, the male/female ratio was exceptionally low (1.23). It was reported earlier that the age distribution has shifted to a lower age level in the years of epidemics; but the present survey data did not differ markedly from those obtained in years when no epidemics were observed. In the observation of monthly distribution, the incidences of typical cases were found to be high in the winter months and low in fall. However, no clear-cut seasonal trends were noted. During the nationwide epidemics of 1982 and 1986, a definite seasonal trend (an increase from the end of winter toward early spring) was recognized but our finding in the present survey was substantiated in the data from the earlier non-epidemic periods.

For the etiology of Kawasaki disease, the infection theory based on past epidemiologic data has been and still is most dominant. Nationwide epidemics occurring three times during the same season at approximately 3-year intervals constitute an important basis to support the infection theory. However, the fact that no signs of an epidemic have been seen for the past 8 years since 1985 does not necessarily support the theory. On the other hand, it should be noted that we still observe incidences of approximately 1% among siblings and a sudden rise in morbidity when maternal immunity ceases to exist after birth.

For the laboratory examinations to be conducted during the acute stage, we added a white blood cell count (the maximum value) and CRP value (the maximum) among the mandatory examinations for the diagnosis of Kawasaki disease. By adding these new items, we planned to observe the distribution of the extent of inflammatory responses during the acute stage and their background so that we may clarify the relationship of the response to the prognosis. Ours is the first nationwide survey by which white blood cell counts and distribution of CRP were investigated. Differences in the standard values associated with the white blood cell counts in each facility may not cause a serious problem but deviations in the standard value for CRP at each laboratory may be worthy of some consideration. However, the facilities responding to the survey are too numerous for standardization of the data. We just have to keep in mind that the results include inter-facility deviations. We found a maximum white blood cell counts in a range of 12,000 to 16,000/µl in one-third of the patients, with 66% of them in a range of 10,000 to 20,000/µl. There was no difference in the distribution between the typical and atypical patients, while it was slightly shifted to the left in the suspected patients. But there was little clinical difference among these 3 groups. The CRP value ranged from 5.0 to 9.9 mg/dl in one-third of the patients (typical, atypical, and suspected groups all included); but as in the white blood cell counts, the distribution shifted to the left in the suspected cases. The distributions of the results in the two laboratory examinations (white blood cell count and CRP level) support the approach that these 3 groups may constitute a single disease unit; but we cannot deny the possibility that the suspected patients (12% of the entire patient population) may include other disease entities similar to Kawasaki disease. We plan to conduct a detailed study on the relationship among white blood cell counts, CRP level, and other test results on the occasion of the next survey.

The survey revealed that the incidence included recurrences in 3% and multiple recurrences in 0.2%. The data indicate that the risk of a repeated recurrence after the second incidence is extremely high (approximately 7%). It may be assumed that those patients who suffer recurrences show abnormal immunological responses to the pathogen or substances derived from the pathogen (such as superantigens and heat-shock protein) at the initial infection and suffer the return of the disease at the second exposure to the pathogen. Those who experienced the return of the disease are likely to develop the disease repeatedly thereafter. Therefore the hypothesis that multiple pathogens are involved is not plausible. For the reasons given above, there is a strong probability of recurrence even if the infection theory is upheld for Kawasaki disease.

Mortality is higher among males (4 times that for females) and among those under 1 year of age (3 times that of those over 1 year). Sequelae involving the heart are also frequent among males. These findings coincided with the results of past surveys.

The present survey clarified the status of the IVGG therapy for patients with Kawasaki disease. The dosages were 1000 mg/kg and 2000 mg/kg for most patients (32% and 21%, respectively). The latter is twice that of the former, which leaves some question about the optimum dosage. The past studies on therapeutic efficacy have been inadequate and there is a definite need for research on optimum delivery methods (e.g., total dosage, single dosage, split administration, and duration of administration). We noted that IVGG administration was initiated on the 8th day following the onset in more than 10% of the patients, which poses another problem related to this therapeutic modality. There are some results that cast a doubt on the efficacy of the treatment when the start of IVGG administration was delayed. There is an urgent need to clarify this question.

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