Epidemiology of Kawasaki Disease in Japan

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Abstract
Kawasaki disease was first described by Dr. Tomisaku Kawasaki in 1967. This disease is an acute, febrile illness primarily affecting infants and children younger than 4 years old. Although this disease is characterized by systemic vasculitis, the etiology is still unknown. To clarify the epidemiologic features of Kawasaki disease, nationwide surveys have been conducted since 1970. Approximately 186,000 patients were identified in 17 surveys completed prior to 2002 based on similar diagnostic criteria. From the results of these surveys, not only the disease distributions, such as annual or monthly changes and geographical shift, but also the clinical characteristics of this disease were clarified. Epidemiologic studies of this disease in Japan provide useful results for physicians and researchers around the world who are involved in treating Kawasaki disease.

Key words  Kawasaki disease, Epidemiology, Nationwide survey, Diagnostic criteria, Distribution, Prognosis

Introduction
Dr. Tomisaku Kawasaki first encountered a 4-year-old boy with the unique clinical characteristics of muco-cutaneous lymph node syndrome (MCLS) in 1961 and described a further 50 cases that had similar characteristics to the first case in the journal Arerugi in 1967.1 Now more commonly known as Kawasaki disease, MCLS is acute self-limited vasculitis that occurs predominantly in infants and children younger than 4 years old. This disease is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral cavity, changes in the extremities, polymorphous exanthema, and nonpurulent cervical lymphadenopathy. Cardiac sequelae, such as coronary arterial dilatation and aneurysms, are the most important issues in this disease. The etiology is still unknown.

To clarify the characteristics of this disease, epidemiologists have contributed to the research since 1970. In this review, we introduce the results from epidemiologic studies conducted in Japan, predominantly from nationwide surveys of Kawasaki disease.

The Diagnostic Guidelines and Nationwide Epidemiologic Surveys of Kawasaki Disease

After publication of the case series on Kawasaki disease by Dr. Kawasaki, a Ministry of Health and Welfare medical research grant in fiscal year 1970 enabled formation of the Kawasaki Disease Research Committee. The group’s first project was a
nationwide survey of the disease, utilizing the “Diagnostic Guidelines of Kawasaki Disease (first edition)” compiled prior to the survey so that uniform and clearly defined criteria would be available to the many pediatricians cooperating in the case collection effort. This principle of epidemiologic surveys is one of the most important procedures to researchers in the field.

Kawasaki disease was not widely known among pediatricians at the time. For a start, the survey aimed to ensure that reported cases were identified on the basis of uniform criteria. In addition, the objective was to make the disease’s existence more widely known.

The diagnostic guidelines succinctly list Kawasaki disease’s main symptoms together with relevant information. For easy understanding, color photographs on the back page illustrate the disease’s main manifestations. Because the descriptions of the main symp-

Table 1 The fifth revised edition of the Diagnostic Guidelines

This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. PRINCIPAL SYMPTOMS

1. Fever persisting 5 days or more (inclusive of those cases in which the fever has subsided before the 5th day in response to therapy)
2. Bilateral conjunctival congestion
3. Changes to lips and oral cavity: Reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
4. Polyphormous exanthema
5. Changes to peripheral extremities:
   - [Initial stage]: Reddening of palms and soles, indurative edema
   - [Convalescent stage]: Membranous desquamation from fingertips
6. Acute nonpurulent cervical lymphadenopathy
   At least five items of 1–6 should be satisfied for diagnosis of Kawasaki disease. However, patients with four items of the principal symptoms can be diagnosed as having Kawasaki disease when coronary aneurysm or dilatation is recognized by two-dimensional echocardiography or coronary angiography.

B. OTHER SIGNIFICANT SYMPTOMS OR FINDINGS

The following symptoms and findings should be considered in the clinical evaluation of suspected patients.

1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly), 2-D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (axillary etc.), angina pectoris or myocardial infarction
2. GI tract: Diarrhea, vomiting, abdominal pain, hydrops of gall bladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
3. Blood: Leukocytosis with shift to the left, thrombocytosis, increased ESR, positive CRP, hypoalbuminemia, increased α2-globulin, slight decrease in erythrocyte and hemoglobin levels
4. Urine: Proteinuria, increase of leukocytes in urine sediment
5. Skin: Redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the finger nails
6. Respiratory: Cough, rhinorrhea, abnormal shadow on chest X-ray
7. Joint: Pain, swelling
8. Neurological: CSF pleocytosis, convulsions, unconsciousness, facial palsy, paralysis of the extremities

REMARKS:

1. For item 5 under principal symptoms, the convalescent stage is considered important.
2. Non-purulent cervical lymphadenopathy is less frequently encountered (approximately 65%) than other principal symptoms during the acute phase.
3. Male: Female ratio: 1.3–1.5 : 1, patients under 5 years of age: 80–85%, fatality rate: 0.1%
4. Recurrence rate: 2–3%, proportion of siblings cases: 1–2%
5. Approximately 10 percent of the total cases do not fulfill five of the six principal symptoms, in which other diseases can be excluded and Kawasaki disease is suspected. In some of these patients coronary artery aneurysms (including so-called coronary artery ectasia) have been confirmed.
The Results of the Past 17 Nationwide Surveys on Kawasaki Disease

Since the first nationwide survey of Kawasaki disease in 1970, 17 surveys have been conducted and data on approximately 186,000 patients (covering a 32-year period ending on December 31, 2002) have been collected. In each survey, the targets were hospitals with 100 or more beds and a pediatric department, which were selected from medical facilities located throughout the country. Starting from the 11th survey, those hospitals specializing in pediatrics and having less than 100 beds were also included. For the selection of these hospitals, the latest edition of “Listing of Hospitals” (compiled by the Ministry of Health and Welfare and published by Igaku Shoin) that was available at that time was used.

These nationwide surveys for Kawasaki disease have been conducted biannually for the past 32 years since 1970 (Table 2). Throughout this period, patients’ data were collected based on generally uniform diagnostic criteria. Although the criteria was updated 5 times, the basic clinical findings described in them remained unchanged, enabling annual comparisons of the data. The surveys were conducted throughout the country, targeting all the facilities with pediatric departments among major hospitals equipped with 100 or more beds. It is plausible to assume that this is the most reliable data available exhibiting epidemiologic features of Kawasaki disease in Japan.

This section focuses on changes in the epidemiologic profile of Kawasaki disease that took place during these 32 years and was noted in the 17 nationwide surveys described above.2–28

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**Table 2 Survey years and number of hospitals in 17 nationwide epidemiologic surveys in Japan**

<table>
<thead>
<tr>
<th>Survey number</th>
<th>Covered years</th>
<th>Number of hospitals</th>
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<tr>
<td>1</td>
<td>1969–1970</td>
<td>1,458</td>
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<tr>
<td>2</td>
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<td>4</td>
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<td>16</td>
<td>1999–2000</td>
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<tr>
<td>17</td>
<td>2001–2002</td>
<td>2,413</td>
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Annual changes in the number of patients by sex are shown in Fig. 1. The total number of patients was reported to be 186,069 (107,876 males and 78,193 females).

Between 1965 and 1986, the number of patients mounted steadily: during this time, sudden outbreaks were noted 3 times, forming high peaks when compared with the statistics of the year before or after (1979, 6,867 patients with an incidence rate of 78.0, 2.1 times the previous year; 1982, 15,519 patients with an incidence rate of 196.1, 2.5 times the year before; and 1986, 12,847, with an incidence rate of 176.8, 1.7 times the preceding year). Between 1987 and 1998, the number of patients increased gradually within a range of 5,000 to 7,000. In 1999, it exceeded 7,000; and in 2000, 8,000. In the last two years, this rising trend appears to be continuing. The sex ratio has been 1.38, according to the surveys.

In examining the annual changes in incidence rate (Fig. 2), the continued drop in the population between the ages of 0 to 4 years must be considered, making the rising trend in incidence rate since 1987 appear more drastic than suggested by the curve representing the number of patients. Compared with a rate of 73.8 in 1987 (the year immediately after the third outbreak), those for 1998, 2000, and 2002 were 111.5 (1.5 times), 141.1 (1.9 times), and 151.2 (2.0 times), respectively.

Due to a lack of knowledge of Kawasaki disease among pediatricians, the rate of responses from the target facilities was low until around 1978, when the number of patients involved in the annual fluctuations perhaps reflected a change in attitude by the pediatricians towards the disease, compounding the actual increase in incidence.
However, triggered by the nationwide epidemic witnessed in 1979, interest in Kawasaki disease among pediatricians intensified. Since the 6th nationwide survey, the response rate has always exceeded 60%; therefore it is believed that since this time, the survey data faithfully reflected the true annual changes in the incidence of this disease. Since 1970, the response rate has been maintained between 60 to 70%. However, compared with ordinary hospitals, the response rate of major hospitals caring for a large number of patients is higher; and most of the patients who initially visited hospitals equipped with less than 100 beds (not targeted in the current surveys) are eventually referred to those with a bed capacity of more than 100. In view of these facts, one can safely assume that since 1979 the surveys encompass more than 80% of the patients in this country.

(2) Monthly changes
When incidence during the last 10 years is examined in quarterly periods (January to March, April through June, July through September, and October through December), the incidence is found to be lower without exception in the fourth quarter for both sexes.

(3) Geographical shift in epidemiologic trends
The 16th nationwide survey recorded more than 7,000 patients in 1999. In 2000, the number exceeded 8,000, which surpassed the 6,867 patients of 1979 (the year of the first epidemic). The geographic difference in incidence was examined for 1999 and 2000: in September and October of 1999, the incidence was slightly higher in Kyushu; in November and December, the area of high incidence spread and a high incidence was noted even on the Japan Sea side of the Tohoku region. In January and February of 2000, the high incidence, which originally occurred mainly in the western part of Japan, spread gradually throughout the country, continuing to spread in March–April, May–June, and July–August. Areas of high incidence rate remained in part of Tohoku in September and October and on the Pacific Ocean side of the country in November and December.

The initial increase in the number of patients occurred in specific areas but spread throughout the country within 3 to 6 months. Similar epidemiologic patterns have been observed overseas, supporting the hypothesis that a viral infection is involved in the cause of Kawasaki disease. No abnormal incidence rates that may qualify as an epidemic were noted between 1987 and 2000. In 1999 and 2000, the observed trend then changed: the incidence rate rose slightly (in 2000, the incidence exceeded that of 1979). Like the pattern in past epidemics, the incidence during this period shifted from one geographic area to another. However, unlike the past pattern, the epidemic had not evidently ended at the time of the conclusion of this study.

(4) Age distribution
With hardly any exceptions since the 1st nationwide survey, the age-specific incidence rate was expressed by a single-peak curve (the peak representing 0 to 11-month-old infants): under one year, 27.8% (males, 28.8%; females, 26.5%) and under 4, 81.7% (males, 82.3%; females, 81.0%). Fig. 3 shows the sex and age specific incidence rates com-
puted from the means of each year from 1991–1996.

The results of the nationwide surveys exhibit the following patterns: the incidence rate for Kawasaki disease is markedly low from birth to 2 months of age, rises suddenly between 3 and 5 months, peaks between 6 and 8 months and 9 and 11 months, and undergoes a sudden decline thereafter. To explain this pattern, the following scenario is cited: micro-organism(s) of unknown pathogenicity commonly exist in the living space of children; and the morbidity among them rises, corresponding to the time when the maternally derived immunity level declines after birth.

(5) Incidence among siblings and recurrences

Questions on family history and recurrences were added in 1977.

The familial incidence has always been around 1%, which is more than 10 times the level expected from the general incidence. The possibility of a risk from common exposure, familial transmission, and common host factors should be considered. The proportion of Kawasaki disease patients whose parents suffered from the same disease was 0.2% in the 16th survey. When compared with parents in the general population, the probability of a history of Kawasaki disease was significantly higher in those parents whose children had the same disease. This suggests that a genetic predisposition to Kawasaki disease may be implicated in its occurrence.

Recurrences were observed in approximately 3%, a rate that varied little over the years. There were some patients who suffered from the disease 3 or more times. The sex ratio for recurrence was 1.6 (the risk of a recurrence for patients who had a history of Kawasaki disease was 1.1; thus no difference was observed vis-à-vis sex). Fatalities were high among those suffering a recurrence [0.9%; 3 times higher than the rate for all cases (0.3%)]. A positive correlation was observed between the recurrence rate and morbidity for season and geographic area. The incidence among siblings was high in those who suffered a recurrence — 3 times higher than the rate for all cases studied. The recurrence rate during an epidemic was 950 in every 100,000 patients, which is 6 times higher than the morbidity rate observed among 0–4 year olds during the same period (150 in every 100,000).

(6) Cardiac sequelae

Questions on cardiac sequelae were added in 1983. Until 1996, the question on the incidence of cardiac sequelae was posed in a “yes” or “no” format, while the sequelae were clearly defined in the survey form as “recognition of dilation of the coronary artery (including aneurysms), coronary artery stenosis (including obstruction), and myocardial infarction or valvular lesions, all developing at least one month after onset.” On the other hand, since 1997 when the 15th nationwide survey was conducted, the question on the sequelae was subdivided into two parts, acute stage cardiac dysfunction (within one month of onset) and cardiac sequelae (occurring at least one month after onset). One should note that some of the symptoms corresponding to acute stage cardiac dysfunction defined above might have been reported as sequelae in the surveys that were conducted up to 1996.

The percentage for those with cardiac sequelae was 16.7% in 1983, which gradually decreased since then to 12.1% (1996), 5.1% (1997), and 5.7% (2000), showing a clear-cut drop between 1996 and 1997. One reason for this phenomenon may be the deviation caused by having created a separate question for acute stage cardiac dysfunction; but it is also due to the tendency for reductions in the development of this dysfunction.

According to the 17th survey, 16.2% of reported patients (18.6% male, 13.0% female) had acute cardiac disorders, the rate being high among infants less than 6 months old and older infants. On the other hand, 5.0%
(6.9% male, 3.8% female) of patients had cardiac sequelae, which is a third of the proportion of acute cardiac disorders for both males and females. In terms of age, the proportions were higher in infants of less than 6 months old and in older children, thus forming a gentle U-shaped curve dipping at the 2 year-old mark. The proportion of patients with acute cardiac dysfunctions included: 12.97% for coronary artery dilatation, 1.96% for aneurysms, 1.58% for valvular lesions, 0.27% for giant aneurysms, 0.05% for coronary stenosis, and 0.02% for myocardial infarctions. The proportion of patients with cardiac sequelae were: 3.13% for coronary artery dilatation, 1.36% for aneurysms, 0.29% for giant aneurysms, 0.31% for valvular lesions, 0.06% for stenosis, and 0.04% for myocardial infarctions.

For the factors contributing to the development of cardiac sequelae, the following have been cited: male sex; age under 6 months or over 7 years; a recurrence of Kawasaki disease; and a low level of serum albumin. To clarify the etiological factors for the development of giant aneurysms, a case-control study was conducted, in which the clinical findings up to 20 days after onset were compared. Subsequently, the following were suspected to be risk factors for the development of a giant aneurysm: a low serum potassium level at admission, low minimum platelet count, a high maximum platelet count, high level of maximum C-reactive protein, low minimum hematocrit level, minimum hemoglobin level, maximum white blood cell count, and late development of minimum albumin level. The incidence of cardiac sequelae was high among recurrent cases, irrespective of the association of cardiac sequelae with the first affliction.

(7) Mortality

Until 1974, the case-fatality rate exceeded 1%, which gradually decreased and remained around 0.1% in the 1990s. The mean for all the surveys is 0.25%. A reduction in fatality rate was evident, which is probably due to the efficacy of gamma-globulin therapy and a relative drop in incidence due to the dissemination of information on this disease among pediatricians and the resultant inclusion of many milder cases in the reports.

Yashiro, et al. observed the 449 fatal cases reported by 1998 (which include the fatal cases plus 40 patients who were alive at the time of the survey but whose death was confirmed later). The results showed a fatality rate of 0.29% (and 0.63%, a particularly high rate among children under one year of age); the male/female ratio was 1.5; extensive use of gamma-globulin treatment served to reduce the fatality rate markedly; and 11.5% of the patients died one year after the initial diagnosis. Nakamura, et al. conducted a follow-up study on 8,417 patients, each diagnosed in one of 52 hospitals during a period between July 1982 and December 1992. They followed-up on these patients until the end of 1999 and reported that the standardized mortality ratio increased during the 2-month acute stage after the first diagnosis; no increase was observed after the acute stage; and the standardized mortality rate among those with cardiac sequelae was high.

(8) Treatment in the acute stage of Kawasaki disease

The use of therapeutic agents — steroid preparations (1974–1990), antibiotics (1974–1990), aspirin (1974–1990), and gamma-globulin (1974–1990) — was investigated. Steroid preparations were used for 53% of cases in 1975 but fell rapidly to 6.3% in 1983, then were almost completely abandoned in the 1990s. Antibiotics were used for 92% of cases in 1974 but their administration was gradually reduced to a 70% level in the 1990s. Aspirin use was around 90% throughout the entire survey period. Gamma-globulin was first dispensed around 1983, exceeded the use of steroids that same year, and has been prescribed for more than 80% of cases since 1992. Its use is now maintained at around 85%.
The dosage of gamma-globulin used for treatment appears to have increased annually. As shown in Fig. 4, the common dosage was 1,000 mg/kg until around 1995 but a dosage of 2,000 mg/kg suddenly became dominant and was applied to more than 50% of the patients in 1998. For the gamma-globulin regimen applied to prevent cardiac sequelae, the following have been cited: initiation soon after onset and administration of a sufficient dosage (2,000 mg/kg), which may be given in massive dosages over a short period, such as 2,000 mg/kg for 1 day or 1,000 mg/kg for 2 days.47,48

Other Epidemiologic Studies on Kawasaki Disease in Japan

(1) Descriptive epidemiology of the patients
1) Geographic distribution
The municipalities neighboring those with high incidence rates also indicated high rates.49,50 The clustering pattern was found in many regions and was also prevalent on the prefectural level, indicating that the prefectures with high incidence rates tended to cluster. The clustering of regions with high incidence rate is probably related to public transportation channels and the movement of people. Simultaneous occurrences on an isolated island and in housing complexes were reported. With regard to the contact between patients, there were instances of specific kindergartens where clustering was evident and others where no such pattern was recognized.51-53 In the 1-year, 4-month period between March 1979 and July 1980, 13 individuals living in a new residential area (population aged 9 or under: 6,300) in the suburbs of Yokohama City contracted the disease. They resided within a 2 km radius of each other; however, Takahashi, et al. found no evident contact among these patients. These patients became affected between November 1979 and July 1980, later than the time when most patients developed the illness during the nationwide outbreak (between March and May 1979).54

2) Occurrences among siblings
Nanri, et al. examined the repeated occurrence of the disease (amounting to 27 times altogether) in 12 recurrent cases.55 The outlines of these cases are as follows: (1) in monozygotic twins suffering the disease four times, the first child occurred when he was 10 months old and the second child when he was 10 months old (with the interval between the two being 9 days). For the second occurrence, the second child was 1 year 10 months old and the first child was 1 year 9 months old (the interval being 18 days); (2) for recurrences in dizygotic twins, the first incidence occurred when the first and second children (a boy and a girl) were 10 months old (the disease developed on the same day), and the second incidence occurred when the boy was 2-years 4 months old and his sister developed aphthous stomatitis 11 days later; and (3) in a brother-sister case, the brother occurred 3 times. A case of Kawasaki disease developing simultaneously in monozygotic twins living in a mountainous region of Kumamoto Prefecture was reported.56 The area offered little contact with people in the surrounding areas. Prior to the development of the disease, 4 older siblings (starting with the oldest) had exhibited cold-like symptoms with a fever. In research conducted by Kumamoto University, it was reported that symptoms occurred 8 times among 3 siblings.
A survey conducted by Tsuchiura Kyodo General Hospital introduced cases of Kawasaki disease occurring a total of 8 times among 3 siblings. The symptoms were first noted in the oldest brother who was going to kindergarten, followed by two younger sisters within one week (with onsets one day apart among the sisters). The number of absentees from the kindergarten and the statistics on the patients visiting local clinics around the same time offered no information to support a marked increase in absenteeism.

3) Similarity to other major infectious diseases

Among the infectious diseases reported in the Ministry of Health and Welfare Infectious Disease Surveillance System, 13 diseases that occur mainly in young children were selected. The number of cases reported per fixed point was compared against cases of Kawasaki disease as reported in the Nationwide Surveys for the same period. Infections such as rubella and exanthema subitum showed a curve similar to that of Kawasaki disease. The peak for hemolytic streptococcal infection, which is the focus of attention as a possible cause of Kawasaki disease, was seen to occur between the autumn and winter.57

4) Cases occurring in hospitals

Kato, et al. in Kurume University reported that 54 days after a patient with Kawasaki disease was admitted to the hospital, another patient who had been admitted in the same room (with congenital laryngomalacia) developed Kawasaki disease. Both patients had coronary artery aneurysms.58 Other cases involving inpatients are rare.

(2) Analysis of the etiological factors

To clarify the possible etiological factors of Kawasaki disease, Kubota, et al. in 1975 conducted a case-control study on mothers of patients with Kawasaki disease, with the cooperation of 128 facilities in 43 municipalities across the country.59 In 295 pairs of patients and the control (patients’ mother selected from her acquaintances controls who had children of the same sex and similar age), 233 attributes were compared, including home environment, medical history, tendency to contract illness, family history, history of inoculations, nutrition during infancy, type of everyday goods used, pregnancy complications, and usage of certain medications. The results can be summarized as follows: a tendency for the patients’ parents to contract tonsillitis, stomatitis, eczema, and conjunctivitis; higher incidences of stomatitis, allergic rhinitis, and chapped lips among the patients and their siblings; no difference in the history of inoculations in comparison with the controls; a slightly higher frequency in early disruption of breast feeding and switching to bottle-feeding immediately or shortly after birth; and a slightly higher incidence of tonsillitis or a more frequent use of antibiotics or anti-allergy drugs when the mothers were pregnant. There was no difference between the two groups when the housing where they resided or other environmental conditions were compared (e.g., type and age of the building, number of floors, type of air conditioning, and presence of pests, animals, and pets). The mothers’ speculations on the cause of the disease included: bathing in the sea or a swimming pool, playing with water, traveling, going for a ride, and enrolling in kindergarten. Kishimoto, et al. conducted an interview with patients admitted to 3 city hospitals and the controls who were matched to the patients in sex and age.60 The results showed that there was no difference in the history of inoculations; the patients’ families were more vulnerable to colds; and there was a tendency among the patients’ mothers not to give colostrum in early infancy and to rely on bottle feeding.

Conclusions

Kawasaki disease was discovered in Japan and is now known around the world. A lot of evidence about this disease, especially that related to epidemiology, has been sent from Japan to the world. Epidemiologic studies
of this disease not only provide clarifying explanations of distribution, but also basic data that are useful for an understanding of etiological and prognostic factors, and, thereby greatly contribute to furthering future research.

References


