

A Summary of the Epidemiologic Surveys on Kawasaki Disease Conducted over 30 years

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Introduction

Kawasaki Disease (acute febrile mucocutaneous lymph node syndrome) is a childhood disease that is prevalent in Japan, and causes coronary aneurysms. Dr. Tomisaku Kawasaki first described this disease in Japan in 1967. In 1970, the Japanese Ministry of Health and Welfare organized the Japan Kawasaki Disease Research Committee to investigate its epidemiologic features, causes, pathological features, and treatment. This committee established diagnostic guidelines for Kawasaki Disease that were used in nationwide surveys that were subsequently conducted. Since then, a total of 16 surveys have been conducted every two years and the 17th survey was conducted in 2003. These nationwide surveys have high response rates and they are highly reliable. In addition to these surveys conducted by the Research Committee, many epidemiologic studies have been conducted. Thus, an enormous amount of data has been collected in Japan. Although the cause of this disease remains unknown, any etiological hypothesis

that is advocated in the future will need to fully account for the epidemiologic findings. The findings collected over 30 years were summarized in a book¹⁾ that was published in 2002 (English version in 2004²⁾). This paper presents some of the epidemiologic features of Kawasaki Disease described in the book.

1. Changes in the number of patients over time

The annual number of patients registered in Japan according to the nationwide surveys is shown in Fig. 1. The number has tended to increase annually and there have been three epidemics, occurring about once every three years. An outbreak is called an epidemic in epidemiology even for non-infectious diseases like Kawasaki Disease. The 1982 epidemic was the largest, involving nearly 16,000 children. Although no further epidemic has occurred since 1986, the gradual increase in the annual number of patients has resumed. In 2000, the number of new cases exceeded 8,000, and this number was ranked third after the first epidemic in 1979. The recent annual incidence

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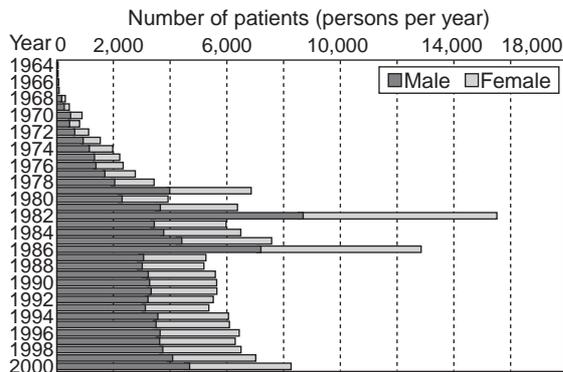


Fig 1 Histogram of the number of patients stratified by year and sex (cited from Reference 2)

rate of Kawasaki disease in children younger than 5 years old is about 140 per 100,000. At each primary school, there will be as many as four pupils for every 600 students who have had a history of Kawasaki Disease. About 170,000 cases of Kawasaki Disease have been reported to date and the number is expected to reach close to 190,000 by the end of 2002. Unreported cases may correspond to about 15% of the total.

2. Age, sex, and recurrence

Patients between the ages of 6 months and 4 years account for about 80% of the total, with a peak in children aged 6 to 12 months, and this pattern has remained unchanged over 30 years. Although rare, Kawasaki Disease has been diagnosed as early as 20 days after birth. Kawasaki Disease has been reported in adult patients of up to 43 years old who have developed the disease, so it is not necessarily a childhood illness. The sex ratio is constant, with a male-to-female ratio of about 1.3:1. Overall, Kawasaki Disease causes coronary lesions about 1.4 times more frequently in male patients, and the incidence of giant aneurysms is about 2.3 times higher in males. Kawasaki Disease recurs in about 3% of the cases, most frequently within 2 years after the initial episode, but rarely after 10 or more years. Patients with up to 5 recurrences have been reported.

3. Other epidemiologic features

The first epidemic in 1979 began in Kyushu and spread to Hokkaido like the flowering pattern of cherry blossoms. In the interim, Kawasaki Disease epidemics occurred in some areas and spread to adjacent regions. This clustering in time and space is characteristic of Kawasaki Disease. Many other characteristics have been clarified by the epidemiologic surveys and these are listed in Table 1.

4. Treatment, incidence of coronary sequelae, mortality, and incomplete type

The principal lesion of Kawasaki Disease is systemic vasculitis. In both Japan and the United States, Kawasaki Disease is the leading cause of acquired heart disease in children. According to the nationwide surveys, immunoglobulin (an immunomodulator) is currently the most common treatment for the disease. Intravenous immunoglobulin (IVIG) was given to about 85% of all patients. Because the efficacy of IVIG is dose-dependent, the total dose for this disease has been recently higher than the usual dose of 1 g/kg, and about 2 g/kg were used in about 70% of the patients. The number of institutions where the total dose was given as a more effective single infusion (instead of divided doses over 5 days) has tended to increase. Coronary lesions occurred during the acute phase in about 18% of patients, a reduction to about half the rate of earlier years when the mainstay treatment was aspirin. The case-fatality rate was initially 2%, and has decreased to the current rate of about 0.1% due to progress in treatment and management. Suspected cases (incomplete Kawasaki Disease), which do not satisfy the major diagnostic criteria, account for about 10% of all cases, and coronary lesions have also been reported in incomplete cases.

5. Prognosis

The long-term prognosis of Kawasaki Disease is unknown. Even patients without coronary sequelae are supposed to be at some risk of

Table 1 Summary of the Epidemiological Features Clarified to Date (cited from Reference 2)

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1. Area
 - Localized simultaneous epidemics in various countries throughout the world
 - Geographic shift of the epidemic and chronological clustering
 - Clustering of areas of high incidence (indicative of a close relationship with the movement of people)
 - Frequent epidemics at the local level
 - Simultaneous incidences in adjacent areas
 - Difference in morbidity rates between northern and southern areas is ambiguous (but the rates tend to be low in southern Kyushu and Okinawa)
Clear-cut differences exist between northern and southern areas for many infectious diseases
 - In-hospital incidence is rare (only about 3 have been reported)
 - Morbidity rate is high in Japan in comparison to neighboring countries
 - In the 1980s, the morbidity rate was high among Hawaiians of Japanese ancestry (3 times the expected value)
 - Many severe cases found in young Caucasian boys
 2. Chronological features
 - Almost no incidences noted before 1960
 - Recent tendency for increase in incidences (the incidence rate in 2000 was the third highest)
 - Epidemics on a nationwide scale (in 1979, 1982, 1986)
 - Seasonal characteristic: peaking from March to May
 - Seasonal occurrence in isolated islands independent of the time of epidemic (Miyakojima: December 1980 to January 1981)
 3. Sex/Age distribution
 - Sex ratio for the risk of developing the disease: male/female=1.3; risk for recurrence=1.1; risk among siblings=1.1
 - Morbidity rate peaks 6 months after birth, after which it decreases with age
 - Decreases in the age and sex ratio of patients during epidemics
 - High incidence of cardiac sequelae and mortality among males and young infants (particularly those under 6 months)
 4. Familial occurrences
 - Risk of siblings contracting the disease during an epidemic: at least 10 times higher than in general population (1% of all patients are siblings)
 - Many cases (at least 50%) occur among siblings within a week of each other
 - For many cases involving siblings, 72% occurs first in the older child
 - Siblings or parents suffer from cold-like symptoms before or after the development of the disease in the family
 - Fatality rate among siblings is high (3 times the average)
 - Frequent family history of tonsillitis, eczema, conjunctivitis, allergic rhinitis, and urticaria in the affected family
 - Abnormal health condition of the mother during pregnancy (e.g., tonsillitis and the use of medication)
 5. Environmental factors
 - Fatigue and changes in environment (travel, swimming in a pool, moving to another home, and having guests), which may trigger the disease
 - Type of housing, number of floors, age of building, and the use of air conditioner have no effects
 - No effects exerted by indoor pests (number of ticks or tick layer) or the presence of domestic pets
 - No effects from insecticides or detergents
 - No effects from parents' occupations
 - Carpet cleaning (results observed in the United States)
 6. Dietary habits
 - No effects from the type of infant nutrition or milk given
 7. Medical history
 - History of frequent contract of cold or allergic rhinitis
 - History of upper respiratory tract infection prior to onset
 - No history of taking any specific medication prior to onset
 - No relationship with inoculation history
 8. Recurrence
 - Recurrence observed in 3% of patients; recurrence often noted within 2 years of the first episode
 - Frequent recurrence among some siblings
 - Recurrence rate among siblings is higher (3 times) than among overall patient population
 - Recurrence rate during an epidemic is at least 6 times that of the morbidity rate during the same period
 - Fatality among recurrent cases is high (3 times the average)
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developing juvenile coronary atherosclerosis. More than 40,000 patients with Kawasaki Disease have already reached adulthood. Because the highest incidence of this disease is found in Japan and it was detected by a Japanese pediatrician, the world has expected Japanese researchers to clarify the prognosis. Accordingly, it is very important to continue the epidemiologic surveys. The latest diagnostic guidelines and photographs showing features of the Kawasaki Disease are available at the

Kawasaki Disease website (<http://www.kawasaki-disease.org>).

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