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Epidemiologic Features of Kawasaki Disease in Taiwan, 2003–2006

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What's Known on This Subject

KD is the leading cause of acquired heart disease in children worldwide. Between 1996 and 2002, the incidence of KD in Taiwan was 66 in 100 000 children. In Taiwan, it occurs more frequently during the summer.

What This Study Adds

Between 2003 and 2006, the incidence of KD in Taiwan was 69 in 100 000 children <5 years of age. Taiwan has the third highest incidence of KD in the world, after Japan and Korea.

ABSTRACT

OBJECTIVE. Kawasaki disease is the leading cause of acquired heart disease in children worldwide. This study characterizes the epidemiology of Kawasaki disease in Taiwan between 2003 and 2006.

METHODS. Using Taiwan's 2003–2006 national health insurance claims, we investigated the epidemiologic features of Kawasaki disease (ICD-9-CM code 446.1) and coronary artery aneurysm formation (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 414.11) and compared the incidences of these diseases with those occurring between 1996 and 2002 in Taiwan and those reported by other countries.

RESULTS. During our 4-year study period, 3877 children and adolescents <20 years of age were hospitalized for Kawasaki disease. Ninety percent of these children were <5 years of age, and the male/female ratio was 1.62:1. The annual incidence of Kawasaki disease was 153 in 100 000 children <1 year of age, 111 in children 1 year of age, 58 in children 2 years of age, 30 in children 3 years of age, 19 in children 4 years of age, and 5.2 in children 5 to 9 years of age. The overall incidence was 69 cases per 100 000 for children <5 years of age. Kawasaki disease recurred in 1.5% of all cases. Kawasaki disease occurred most frequently in the summer and least frequently in the winter. Coronary artery aneurysm occurred in 7.2% (279 of 3877) of all Kawasaki disease cases.

CONCLUSIONS. The overall incidence of Kawasaki disease was 69 in 100 000 children <5 years of age between 2003 and 2006 in Taiwan, comparable with the incidence of 66 in 100 000 children between 1996 and 2002. Taiwan has the third highest incidence of Kawasaki disease in the world, after Japan and Korea. In Taiwan, it occurs more frequently during the summer. *Pediatrics* 2009;123:e401–e405

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Key Words
Kawasaki disease, incidence, seasonality, Taiwan

Abbreviations
KD—Kawasaki disease
CAA—coronary artery aneurysm
NHI—national health insurance
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
SARS—severe acute respiratory syndrome
IVIg—intravenous immunoglobulin

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SINCE DR TOMISAKU Kawasaki characterized the complex pattern of illness known as Kawasaki disease (KD) in 1967 in Japan,[1] it has been found to be the leading cause of pediatric acquired cardiac disease worldwide, especially in developed countries. This acute illness presents as systemic inflammation and occurs as fever lasting >5 days, with conjunctival and oral mucosa changes, fissured lips, cervical lymphadenopathy, skin rash, and palm/sole erythema/induration.[1] The most serious complication of KD is coronary artery aneurysm (CAA). Children <5 years of age are the most susceptible population, with a higher incidence reported for boys.[2–4]

According to recent epidemiologic studies, Asian populations have a much higher incidence of KD. Japan has the highest annual incidence in the world (137.7 per 100 000 children <5 years of age between 1999 and 2002),[2] followed by Korea (105 per 100 000 children <5 years of age between 2003 and 2005),[3] and Taiwan (66 per 100 000 children <5 years of age between 1996 and 2002).[4] Beijing has reported an increased incidence, increasing from 40.9 per 100 000 persons in 2000 to 55.1 in 2004, compared with the increase from 18.2 to 30.6 per 100 000 that occurred there between 1995 and 1999.[5] In Hong Kong, the average annual incidence was 39 per 100 000 between 1994 and 2000.[6] In Western countries, the incidence of KD is significantly lower. Canada reported an annual incidence of 20.6 per 100 000 for the period between 1998 and 2000.[7] The United States had an annual incidence of 17.1 per 100 000 in 2000, although Asian and Pacific Islander children there had much higher incidence (39 per 100 000) than the other ethnic groups,[8,9] and the KD incidence of Japanese American children living in Hawaii was even higher, up to 197.7 per 100 000.[10] New Zealand had an annual incidence of 8.6 per 100 000, and there, children of East Asian ethnicity had a higher incidence (12.2 per 100 000).[11] In Europe, Ireland reported an annual incidence of 15.2 per 100 000 between 1996 and 2000.[12] A 20-year survey showed Denmark to have an annual incidence of 3.6 per 100 000 between 1981 and 2000.[13] All of these studies reported a higher incidence of KD in boys. However, the differences in rates reported in these studies should be considered with some caution as they may be affected by ethnicity, geographic regions, size of the database, study periods, and methods of data collection.

In Taiwan, a national surveillance of KD was started in 1996 and was based on data collected from Taiwan's national health insurance (NHI) database.[4] Taiwan's NHI, implemented in 1995, covers most of the medical care costs of over 96% of its population.[14] Therefore, this database can serve as a rich source of nationwide data.

Because the incidence of KD has been rising, particularly in Asia, and recent epidemiologic changes have not been studied in Taiwan, we used data collected from Taiwan's NHI health care database to analyze the epidemiologic characteristics of KD and compare our latest results with those reported for the period between 1996 and 2002.

METHODS

Taiwan has a population of 22.9 million people and land area of 36 188 km^2. Its population density is 633/km^2. Taiwan's NHI covered most of the health care costs for 98% of its population in 2006;[14] the remaining 2% of it population were living in foreign countries or in families with monthly household incomes <\$1000 US.[15] Taiwan's NHI database includes health care data collected from over 95% of the hospitals in Taiwan for >96% of the population receiving health care. From this database, we collected claims data submitted for children <20 years of age hospitalized with a major diagnosis or second diagnosis of KD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 446.1) between 2003 and 2006. We analyzed these hospitalizations by age, gender, month of hospitalization, and year. In addition, they were analyzed for duration of stay and cost of care.

The annual incidence of KD was calculated by dividing the number of KD-associated hospitalizations by the population of children of the same age as reported by Taiwan's 2003 and 2006 census. The annual incidence of KD was reported as the number of KD hospitalizations per 100 000 children. The database also included patients with KD who were also diagnosed as having CAA (ICD-9-CM code 414.11). The rate of CAA was calculated by dividing the number of cases with both KD and CAA by the total number of patients with KD. CAA was defined as coronary artery >3 mm in diameter in children <5 years of age and >4 mm in diameter in children >5 years of age. Recurrence of KD was defined as a period of >1 month between 2 hospitalizations to prevent recounting the KD cases with exacerbations that occurred 1 to 2 weeks after original discharge. Our current nationwide database lacks the information regarding coronary artery dilatation or pericardial effusion, and thus it was not feasible to provide the data on these 2 parameters.

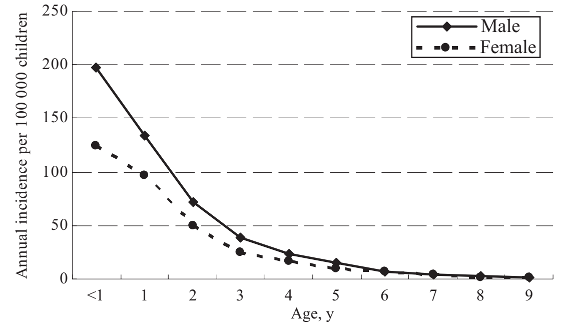

FIGURE 1
Incidence of KD in Taiwan according to gender and age between 2003 and 2006.

Data are expressed as mean (SD), median (range), or percentage (number). The annual incidence of KD was calculated by using census data as the denominator. The differences among continuous variables were measured by a *t* test. The differences in annual incidences among various age groups, the differences in annual incidences between different years, and the differences in seasonal distribution were analyzed with a goodness-of-fit χ^2 test. The difference in male/female ratio between infants and children who were >1 year of age was measured by using a Pearson χ^2 test. A P value of <.05 was considered significant. All statistical operations were performed by using SAS 9.1 statistical software (SAS Institute, Inc, Cary, NC).

RESULTS

Incidence of KD, Recurrence, and Gender Difference

Between 2003 and 2006, 3877 children and adolescents <20 years of age were hospitalized for KD. Mean age (± SD) was 1.7 ± 2.3 years (median: 1.0 year). The male/female ratio was 1.62:1. As can be seen in Fig 1, regardless of age, there was a significantly higher incidence of KD in boys than in girls ($P < .01$).

Fifty-nine (1.5%) of the 3877 claims had recurring KD. Of the 59 cases of recurring KD, 52 cases had 2 attacks and 7 cases had 3 attacks. Fifty-two (80%) of the 59 cases had a second attack within 2 years of their first episode. The median interval between the 2 attacks was 349 days (range: 35–1175 days).

Age-Specific Annual Incidence

KD occurred predominantly in children <5 years of age (90%; $P < .01$). The annual incidences in children <5 years of age and 5 to 9 years of age were 69 and 5.2 per 100 000, respectively. As can be seen in Fig 2, the annual incidence was 153 per 100 000 in children <1 year of age, averaging 7.3 ± 2.7 months ($P < .01$) and peaking

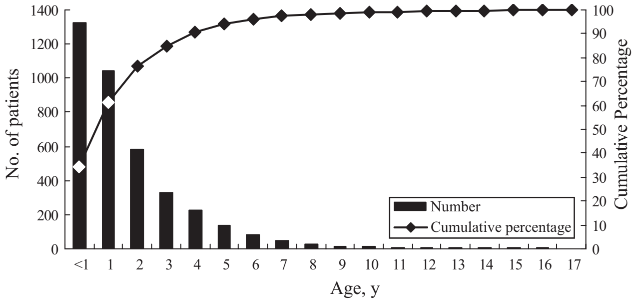

FIGURE 2
Age distribution and cumulative percentage of KD between 2003 and 2006.

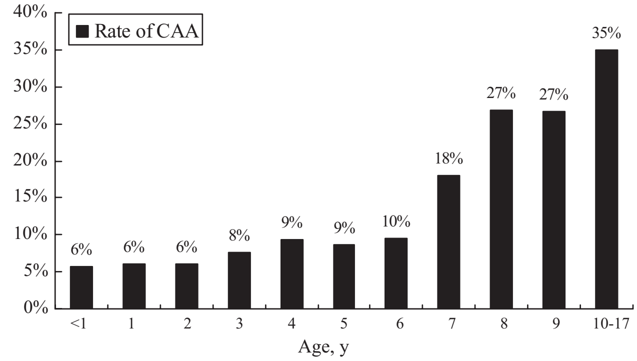

FIGURE 4
Age-specific rates of CAA among patients with KD.

at 11 months (Fig 3). The annual incidence was 57 per 100 000 in infants ≤3 months of age, significantly lower than the 184 per 100 000 for infants between the ages of 4 and 11 months ($P < .001$).

In general, the annual KD incidence decreased with age. It was highest in infants (153 per 100 000), followed by children 1 year of age (111 per 100 000) and children 2 years of age (58 per 100 000). The incidence was 30 per 100 000 and 19 per 100 000 in children 3 and 4 years of age, respectively ($P < .01$). The annual incidence dropped to 5.2 per 100 000 for children between 5 and 9 years of age.

There were no significant changes in annual incidence of KD in children under 5 years of age during our study period, 2003 to 2006 ($P = .94$). The incidences for each year were 60, 67, 75, and 77 per 100 000 in 2003, 2004, 2005 and 2006, respectively. During these 4 years, the lowest incidence was in 2003, the same year as the severe acute respiratory syndrome (SARS) outbreak in Taiwan.

Rate of Coronary Artery Aneurysm

Two hundred seventy-nine (7.2%) of the 3877 cases of KD also developed CAA, with a significantly greater incidence among boys than girls (7.5% [179 of 2394] vs 4.9% [72 of 1482]) ($P < .001$). We found no significant difference in the rate of CAA from year to year (7.2%, 6.6%, 6.6%, and 8.4% in 2003, 2004, 2005, and 2006, respectively) ($P > .05$). However, we did find that the age-specific rates of CAA increased with age in this population of KD cases (Fig 4), suggesting that the older the patient with KD, the greater the likelihood of CAA.

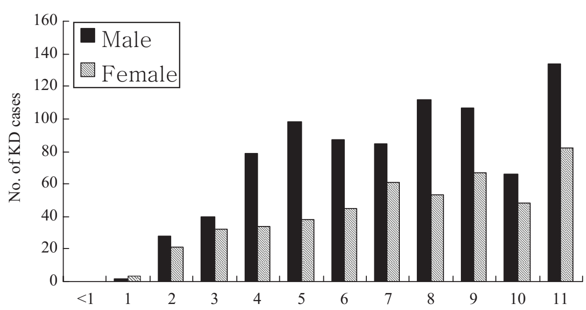

FIGURE 3
Age and gender distribution of patients with KD <1 year of age.

Seasonal Distribution

Figure 5 shows monthly distribution of KD cases. KD occurred most frequently in the summer (28.3%, May to July), followed by the spring (26.7%, February to April), and autumn (24.4%, August to October). The lowest incidence occurred during the winter (20.6%, November to January) ($P < .05$). The incidence of KD in May 2003 (during the SARS outbreak in Taiwan) was relatively low compared with the incidences in May of the other years.

Medical Expense and Duration of Hospitalization

The average number of days the cases were hospitalized was 5.5 ± 4.9, and average expense was 47 897 ± 38 188 new Taiwan dollars (~$1558 US). Approximately 57% of the medical expense was used for drugs, which averaged 27 151 ± 23 256 new Taiwan dollars (~$905 US) and included the cost of intravenous immunoglobulin (IVIg). For KD treatment and retreatment in Taiwan, IVIg is the consensual first-line treatment. For refractory KD cases, no consensus has been reached regarding its management in Taiwan. Because our NHI covers the total expense of IVIg treatment, all the medical centers or hospitals (137 medical centers and hospitals in this study) in Taiwan administer IVIg plus aspirin, and there is no difference in the practice of KD treatment among these centers and hospitals.

DISCUSSION

This study found a higher incidence of KD in children <5 years of age, boys (male/female ratio: 1.62:1), and during the summer months between 2003 and 2006. A comparison of 2 studies found little difference in incidence between our study period (69 per 100 000 persons) and that reported by a previous study between 1996 and 2002 (66 per 100 000 persons).[4] There was not much difference in the recurrence rates and the rates of CAA between the 2 study periods (1.5% vs 1.3% and 7.2% vs 7.3%, respectively).

Like other studies, we found a higher incidence of KD in boys, during certain seasons, in children <5 years of age, and in Asian children (Table 1).[2–12] Taiwan and Korea have the highest incidence of KD in the summer, Beijing and Hong Kong in the spring and summer, and Japan in Jan-

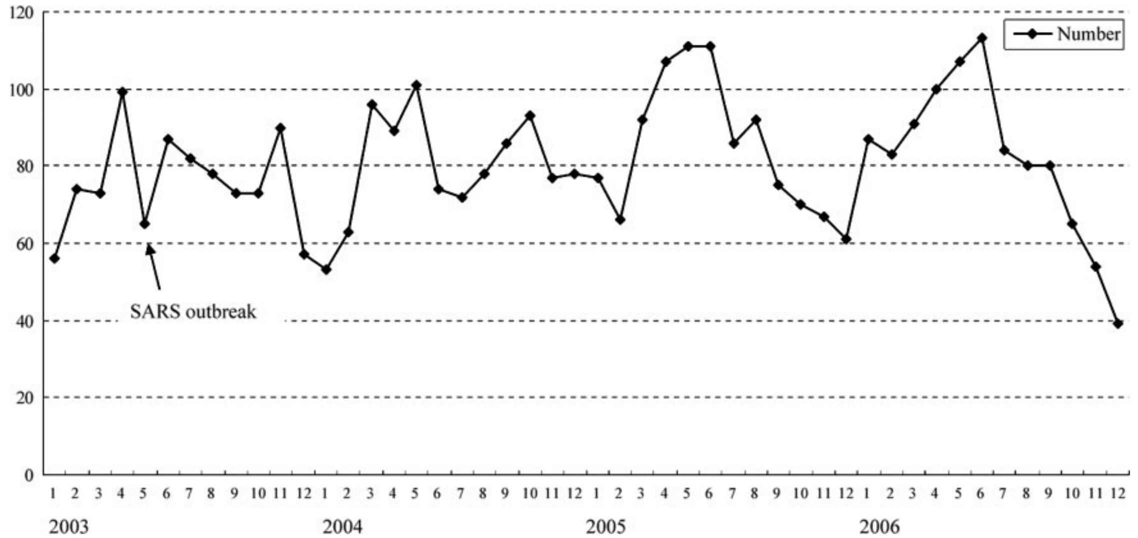

FIGURE 5
Monthly distribution of KD incidence. Between 2003 and 2006, the highest incidence occurred between April and June.

uary and summer.[2–6] Studies from Europe and Canada report a higher incidence in the winter months.[7,12] Although the period may not be the same, there is seasonal clustering. In a 14-year study in Japan, Burns et al[16] clearly demonstrated the seasonality and temporal clustering of KD. Such seasonality and temporal clustering suggests that different infectious diseases or other environmental factors might trigger this clustering presentation. Their study group could not detect a significant increase in the number of viral infections that would match the seasonality they found.[16] However, based on clinical presentations of KD, temporal and family clustering, and seasonality, there may be a possible linkage between KD and infection.[17] That KD hospitalizations were reduced during the SARS outbreak (May 2003) in our study also suggests the possibility that KD is caused by infection. It would be reasonable to assume that if the limitation of people's social activities and the hygiene campaign that took place during the SARS outbreak hindered the transmission of the infectious disease SARS, then KD may also be caused by an infection, if KD

TABLE 1 Comparison of KD Characteristics Among Countries

Country	Authors	Period	Incidence per 100 000 Children <5 y of Age	Male/ Female Ratio	Peak Season/ Month	Peak Age, mo	Recurrence, %	CAA, %	Data Source
Japan	Yanagawa et al[2]	1999–2002	137.7	1.3:1	Jan, Jun–Aug	9–11	NA	17.2	Questionnaire
Korea	Park et al[3]	2003–2005	105	1.52:1	May–Jul	6–12	2.0	18.8 (dilatations: 18, aneurysms: 2.5)	Questionnaire
Taiwan	Chang et al[4]	1996–2002	66	1.70:1	May–Jul (Summer)	7	1.3	7.3% (aneurysm)	Taiwan's NHI
China, Beijing	Du et al[5]	2000–2004	40.9–55.1	1.83:1	Spring and Summer	12	1.4	20.6 (aneurysm: 4.3)	Questionnaire
China, Hong Kong	Ng et al[6]	1994–2000	39	1.7:1	Spring and Summer	NA	NA	5	Questionnaire
Canada	Newburger et al[7]	1998–2000	20.6	2.03:1	Dec–Jan	NA	NA	4.1	Canadian Institute of Health Information
United States	Holman et al[8]	2000	17.1	1.5:1	NA	NA	NA	NA	Kids' Inpatient Database
	Belay et al[9]	1994–2003	NA	1.5:1	Jan–Mar	NA	NA	12.9	National Surveillance System
Ireland	Lynch et al[12]	1996–2000	15.2	2.33:1	Nov–Jan	NA	NA	4.6	Ireland's Hospital In-Patient Enquiry database
New Zealand	Heaton et al[11]	2000–2001	8.0	1.7:1	Mar–May (Autumn)	NA	NA	26	New Zealand Paediatric Surveillance Unit
Denmark	Fischer et al[13]	1981–2004	3.6	1.58:1	Nov–Jan	4–6	NA	2.3	Danish National Patient Registry

NA indicates not available.

hospitalizations were also reduced during this time. This is only conjecture, for the latest research reports on KD do not irrefutably associate KD with infectious agents.[18–22]

In large-scale studies in East Asia, the percentage of coronary artery dilatation is reported to be around 18%,[3] and the complication rate of CAA ranges from 2.5% to 7.2%.[3–5] In the early course of KD, cardiac involvement results in a dilatation of the coronary artery that in most cases is transient under treatment and will not proceed to CAA formation. If CAA formation is found, long-term follow-up is necessary. A 10- to 21-year follow-up study reported that 55% of coronary aneurysm showed regression, although ischemic heart disease developed in 4.7%, myocardial infarction in 1.9% and death occurred in 0.8% of patients.[23] Our study found that CAA gradually increased with age. Belay et al[9] also reported a higher proportion of children <1 year of age and children 9 to 17 years of age to have coronary artery abnormality. Delayed diagnosis or treatment of KD in age groups with a lower incidence of KD might be the cause of this specific finding. Therefore, enhancing awareness of KD and coronary artery abnormality may help minimize the complication rates of coronary artery involvement.[24–26] In the regions with a low incidence of KD, coronary artery involvement is much lower (2.3%–5%).[6,8,12,13] There may be a genetic basis explaining the ethnic differences, although this has not been confirmed. Because the size of the database or content of questionnaires used by many of the studies might confound estimates of incidence of coronary artery complications, additional studies on differences in incidence of coronary artery complications are needed.

CONCLUSIONS

We found that Taiwan has the third highest incidence of KD worldwide, behind Japan and Korea, and that KD occurs more frequently in boys, in children <5 years of age, and during the summer months.

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