Kawasaki Syndrome and Risk Factors for Coronary Artery Abnormalities

United States, 1994–2003

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Background: Kawasaki syndrome (KS) causes significant morbidity among children in the United States and other countries and can result in a range of cardiac and noncardiac complications.

Methods: To describe the occurrence of KS in the United States and risk factors for the development of coronary artery abnormalities (CAA), national KS surveillance data were analyzed for patients with KS onset during 1994–2003. The surveillance is a passive system, and information is collected on a standardized case report form.

Results: During 1994 through 2003, 3115 patients who met the KS case definition were reported to the national KS surveillance system. The median age of KS patients was 32 months; the male-female ratio was 1.5:1. Nearly one-third (31.8%) of the cumulative number of KS cases occurred during January through March. During the study period, 362 (12.9%) of 2798 KS patients had CAA. The proportion of patients with CAA increased from 10.0% in 1994 to 17.8% in 2003. Age younger than 1 year and 9–17 years, male sex, Asian and Pacific Islander race and Hispanic ethnicity (a previously unidentified risk factor) were significantly associated with the development of CAA.

Conclusions: The increase in CAA was attributed to widespread use of the criteria of de Zorzi et al, resulting in increased recognition of coronary artery dilatations. The factors contributing to a higher risk of CAA, such as delayed treatment, particularly among Hispanics, need to be investigated.

Key Words: Kawasaki disease, Kawasaki syndrome, surveillance, epidemiology, complications, children

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Kawasaki syndrome (KS), an acute febrile vasculitis of unknown etiology, was first described in the 1960s by Dr. Tomisaku Kawasaki in Japan.[1–4] It occurs worldwide and primarily affects younger children, particularly those younger than 5 years of age. A higher incidence of KS among children of Asian ancestry has been consistently reported.[5–7] The incidence of KS among children younger than 5 years of age in Hawaii is >2 times higher than the incidence among children in the contiguous United States.[6,7] A recent study of KS in Hawaii indicates that the incidence of the disease may differ among various Asian populations.[7] The incidence appears to be highest among children in Japan and Japanese-American children living in Hawaii, followed by Hawaiian, Chinese-American, Korean-American, and Filipino-American children living in Hawaii, and Taiwanese and Chinese children living in Asia.[7–11]

Patients with KS present with clinical signs and symptoms associated with generalized vasculitis and show laboratory evidence of a systemic inflammatory response.[4] These clinical and laboratory findings, along with other epidemiologic features, are considered to be compatible with an infectious etiology. However, many studies searching for the etiologic agent of KS have not consistently identified a specific infectious agent.

Although KS is primarily self-limiting, the disease causes significant morbidity in most patients and can result in a range of cardiac and noncardiac complications.[2,12] Some of these complications may lead to a prolonged duration of illness, potential long term effects and death in ~0.1% of patients. The most serious complications of KS are related to abnormalities of the coronary arteries, including luminal dilatations and aneurysm. Coronary artery abnormalities (CAA) can occur in >20% of untreated KS patients.[2,4,12] The widespread use of intravenous immunoglobulin (IVIG) to treat KS patients early in the course of the disease has resulted in a marked reduction in the rate of CAA.[12] However, KS remains the leading cause of acquired heart disease among children in the United States and Japan.

In this study, national KS surveillance data were analyzed for patients with KS onset during 1994–2003. The epidemiologic characteristics of the patients, seasonal occurrence of KS, trends in the occurrence of cardiac complications and risk factors associated with the development of CAA were examined.

METHODS

The Centers for Disease Control and Prevention (CDC) has maintained a passive surveillance for KS in the United States since 1976.[13] KS patients are reported to CDC by using a standardized case report form, which has been periodically revised (last revision in 2004). The case report form is available at the CDC website: http://www.cdc.gov/ncidod/diseases/kawasaki/index.htm. Information collected on the form includes personal demographics, such as age, sex, race

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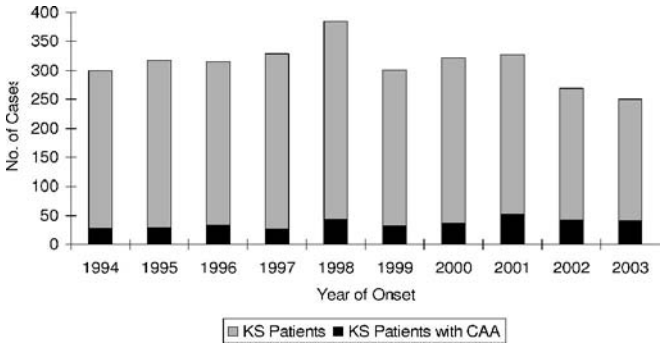

FIGURE 1. Number of KS patients and patients with coronary artery abnormalities (CAAs) by year of illness onset, United States, 1994–2003.

and residence, clinical signs and symptoms and KS complications and outcome. Information collected on KS patients has been maintained in a computerized database since 1984. Despite efforts to ensure full completion of these forms, some of them are not completely filled out.

Patients were included in the study if they met the CDC epidemiologic case definition for KS and had illness onset during 1994 through 2003. To meet the case definition, patients should have fever lasting ≥5 days (or fever until the date of administration of IVIG if it is given before the fifth day of fever) and the presence of at least 4 of the following 5 clinical signs: rash; cervical lymphadenopathy (at least 1.5 cm in diameter); bilateral conjunctival injection; oral mucosal changes; and peripheral extremity changes.[14] Patients whose illness did not meet the above KS case definition but who had fever and coronary artery abnormalities were classified as having atypical or incomplete KS; they were not included in the analysis.

Statistical analyses were performed with the use of SAS version 9.0 (SAS Institute, Cary, NC). Risk ratios with 95% confidence limits were calculated.[15] Characteristics that were significantly associated with the development of CAA were further examined by fitting a series of hierarchical logistic regression models.[15]

RESULTS

During 1994 through 2003, a total of 3689 presumptive cases of KS were reported to CDC; 3115 (84.4%) of the patients met the case definition for KS, and 90 (2.4%) met the case definition for atypical case. The 3115 KS patients were reported from 40 states and the District of Columbia. A majority of the KS patients [2459 (78.9%)] were reported from 6 states: California, Illinois, Michigan, New York, Ohio, and Virginia. The number of reporting states declined from a high of 29 in 1994 and 1996 to 11 in 2002. For the period 1994–2002, the number of reported KS patients ranged from 269 in 2002 to 385 in 1998 (Fig. 1); reports for 2003 are less complete.

Of the 3076 KS patients whose sex was reported, 1852 (60.2%) were boys; the male-female ratio was 1.5:1. Children younger than 24 months of age accounted for 1105 (36.0%) of 3070 KS patients with known age, and 2442 (79.5%) of the patients were younger than 5 years of age. The median age of KS patients was 32 months. Among the 2717 KS patients whose race was reported, most patients (1592; 58.6%) were white, 585 (21.5%) were black, 421 (15.5%) were Asian and Pacific Islander, 10 (0.4%) were American Indian/Alaska Native and 109 (4.0%) were other races. Race information was not reported for 398 (12.8%) of the 3115 KS patients. In the 2000 census data, whites comprised ~71% of the U.S. population younger than 18 years of age, blacks 16%, Asian and Pacific Islanders 4% and American Indians/Alaska Natives 1%.[16] This indicates that blacks and Asian and Pacific

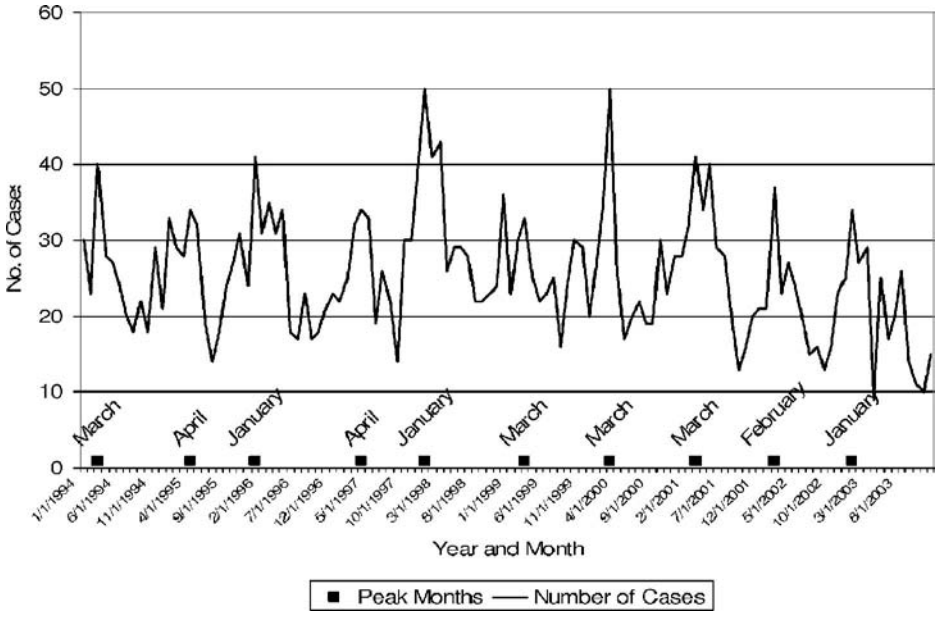

FIGURE 2. Number of KS patients by month and year of onset reported to the national KS surveillance system, United States, 1994–2003.

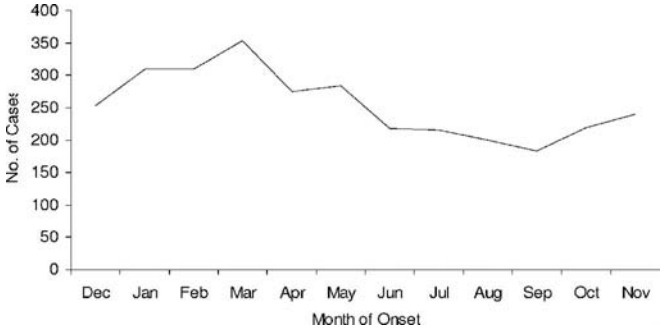

FIGURE 3. Cumulative number of KS patients by month of onset, United States, 1994–2003.

Islanders were overrepresented among KS patients reported to the surveillance system. The overrepresentation of these groups did not change when the analysis was limited to the KS patients and population in the 6 states from which the majority of patients were reported. During the study period, the peak annual number of KS patients occurred in January, February, March or April (Fig. 2). Nearly one-third (31.8%) of the cumulative number of KS patients occurred during January through March (Fig. 3). The lowest number of patients occurred primarily in August and September.

The most common clinical sign reported among KS patients was oral mucosal changes (98.9%) followed by rash (97.9%), bilateral conjunctival injection (97.4%), peripheral extremity changes (92.8%) and cervical lymphadenopathy (65.3%). By definition, all patients had fever, but 223 (7.2%) had fever for <5 days in conjunction with IVIG treatment before the fifth day of fever. Among the KS patients with available information, 3006 (98.8%) of 3041 patients were hospitalized, and 2944 (97.9%) of 3007 patients received IVIG treatment. About one-third of the patients treated with IVIG received the treatment before the fifth day of illness.

During the study period, 362 (12.9%) of the 2798 KS patients whose cardiac findings were reported had CAA. The proportion of KS patients with CAA showed an increasing trend during the 10-year surveillance period ($P < 0.0001$) (Fig. 4). The proportion increased from a low of 10.0% in 1994 to 17.8% in 2003. This increase was primarily the result of an increasing trend in the proportion of KS patients with coronary artery dilatations (Fig. 4). The proportion of patients with coronary artery aneurysms was relatively stable during the surveillance period. A significantly higher proportion of boys than girls developed CAA, 15.3 and 9.5%, respectively (Table 1). Likewise a significantly higher proportion of children younger than 1 year of age (17.2%) and 9–17 years of age (20.0%) had CAA than children 1–8 years of age (11.8%) (Table 1). Among racial and ethnic groups, KS patients who are Asian and Pacific Islanders (18.5%) or Hispanics (17.1%) had the highest proportion with CAA. Patients with recurrent KS were more likely to have CAA than those without recurrent KS (Table 1). A multivariate logistic regression analysis indicated that age younger than 1 year and 9–17 years, male sex, Asian and Pacific Islander race and Hispanic ethnicity were significant risk factors for the development of CAA. These variables remained significant after controlling for IVIG treatment. When the analysis was limited to patients with coronary artery aneurysm, a higher proportion of Hispanic patients had aneurysm than patients who are not Hispanics (risk ratio, 1.53; 95% confidence limits, 0.97, 2.40). Although not statistically significant, a higher proportion of Asian and Pacific Islanders (5.2%) had coronary artery aneurysm than whites (4.1%).

The most common noncoronary artery complications reported among the 3115 KS patients were arthritis or arthralgia [238 patients (7.7%)], pericarditis or pericardial effusion (193 patients (6.2%)], meatitis or sterile pyuria [146 patients [4.7%]), and aortic or mitral regurgitation (134 patients

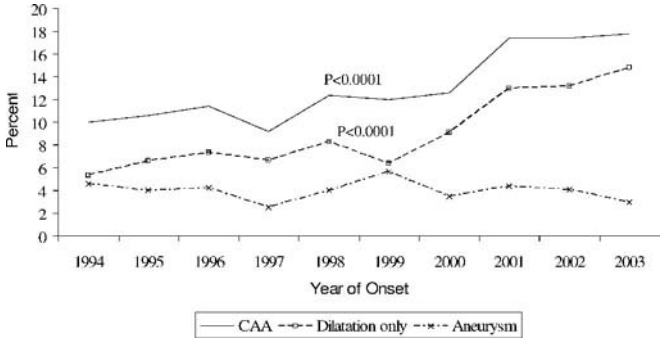

FIGURE 4. Percent of KS patients with CAA, coronary artery dilatations and coronary artery aneurysms, United States, 1994–2003.

TABLE 1. Risk Factors Associated With the Development of CAAs Among KS Patients Younger Than 18 Years of Age Reported to the National KS Surveillance System, United States, 1994–2003

Characteristic	No. With CAA/Total*	% With CAA	Risk Ratio
Age (yr)			
<1	81/471	17.2	1.46 (1.16, 1.84)†
1–8	257/2187	11.8	Reference
9–17	20/100	20.0	1.70 (1.13, 2.56)
Sex			
Male	257/1677	15.3	1.61 (1.30, 2.00)
Female	103/1085	9.5	
Race			
Asian and Pacific Islander	71/383	18.5	1.59 (1.24, 2.06)
White	166/1428	11.6	Reference
Black	55/532	10.3	0.89 (0.67, 1.19)
American Indian/Alaska Native	2/9	22.2	1.91 (0.56, 6.54)
Other	12/97	12.4	1.06 (0.61, 1.84)
Ethnicity			
Hispanic	82/481	17.1	1.28 (1.01, 1.63)
Not Hispanic	195/1469	13.3	
Recurrent KS			
Yes	14/55	25.5	2.02 (1.27, 3.21)
No	308/2439	12.6	

*The denominators represent patients whose CAA status in a given category is known.

†Numbers in parentheses, 95% confidence limits.

TABLE 2. Non-Coronary Artery Complications Among KS Patients Reported to the National KS Surveillance System, United States, 1994–2003

Complications	No. of Patients	%*
Arthralgia or arthritis	238	7.7
Pericarditis or pericardial effusion	193	6.2
Meatitis or sterile pyuria	146	4.7
Aortic or mitral regurgitation	134	4.3
Hepatitis or hepatomegaly	95	3.1
Gall bladder hydrops	72	2.3
Myalgia or myositis	67	2.2
Aseptic meningitis	42	1.4
Iritis or uveitis	30	1.0
Congestive heart failure	12	0.4
Hearing loss	7	0.2
Myocardial infarction	3	0.1

*The denominators could vary because information on complications was not completed for all patients.

(4.3%)] (Table 2). Recurrence of KS was reported in 57 (2.1%) of 2730 patients, and 3 patients (0.1%) died of KS during the 10-year surveillance period. About one-third (31.5%) of the patients with recurrent KS were Asian and Pacific Islanders, and one-half (50.0%) were white.

DISCUSSION

Analysis of national KS surveillance data for the period 1994–2003 did not detect a nationwide outbreak of KS similar to that reported for 1984–1985.[17] The epidemiologic characteristics of KS patients reported to the KS surveillance system were similar to those reported in many other studies.[8,9,11,18] Although the number of reported KS cases did not substantially increase during the 10-year surveillance period, the proportion of KS patients with CAA showed an increasing trend, particularly after 1999. As shown in Figure 4, the increase was clearly the result of an increase in the proportion of patients with coronary artery dilatations, and not coronary artery aneurysms. The increasing trend in coronary artery dilatations is most likely a result of their increased recognition caused by a wider application of the criteria developed by de Zorzi et al.[19] These criteria, first published in 1998, correlate coronary artery internal diameter with patients' body surface area, leading to recognition of coronary artery dilatations that previously would have been undetected.

The proportion of patients with CAA was higher among boys, patients with recurrent KS and patients younger than 1 year and 9–17 years of age. The proportion of Asian and Pacific Islanders and Hispanic children with CAA was also high. To our knowledge, the significantly higher proportion of CAA identified among Hispanics has not been previously reported in published studies. A similarly elevated risk of CAA among Hispanic children was identified in an unpublished study in San Diego, CA (J. C. Burns, MD, personal communication, 2005). Delayed diagnosis and treatment of KS were suggested as contributory factors to the increased risk of CAA among Hispanic children. In our analysis, it was not possible to assess the impact of delayed IVIG treatment because information on the timing of IVIG administration was not available. However, the higher proportion of Hispanic children with coronary artery aneurysm observed in our study supports the conclusion that delayed diagnosis and treatment may have been a major contributory factor. Efforts to minimize the higher risk of CAA should include education of physicians providing primary pediatric care to Hispanic children about the need for early diagnosis or referral of KS patients and provision of culturally appropriate education to Hispanic communities about KS and its potential adverse outcomes.

Children of Asian ancestry have a higher incidence of KS than other race groups.[7,8] The present study indicates that they might also have a higher risk of developing CAAs. The proportion of Asian and Pacific Islander children with CAA (18.5%) was significantly higher than that for white or black children. This proportion was similar to that reported for children in Japan (≥20.1%), Korea (21.0%), and Beijing (21.5%) and Shaanxi Province (19.0%), China.[8,9,18,20]

A number of other noncoronary artery complications were reported among the KS patients. Noncoronary cardiac complications included pericarditis, valvular regurgitation and congestive heart failure. The most common noncardiac complication was arthritis or arthralgia followed by otitis. Although KS cases occurred throughout the year, a clear seasonal pattern of KS occurrence during winter and spring was seen among the cases reported to the national surveillance system. The peak of KS occurrence appears to be during January through March. A striking seasonal variation in the occurrence of KS has also been reported in Japan.[21]

Our study has several limitations. The KS patients reported annually to the surveillance system represent ~10% of patients diagnosed with KS in the United States. However, the similar epidemiologic characteristics of patients in our study with that of previous studies indicate that our findings can be generalized to other KS patients. In addition, the large number of patients from multiple years included in our study (>3000 patients during a 10-year period) should provide robust information about risk factors for the development of CAA. In some instances, KS patients with more severe illnesses (eg, patients with CAA) might be selectively reported to the surveillance system. This might have had an effect of masking the strength of association of a particular risk factor with the development of CAA.

In summary, the national KS surveillance system is an important tool to monitor the possible occurrence of nationwide KS outbreaks and to monitor the trend of cardiac complications among all KS patients and specific racial and ethnic groups. The widespread use of the method developed by de Zorzi et al might have contributed to the identification of KS patients with coronary artery damage who could have been undetected in the past. These patients might be potentially at risk for long term coronary artery disease and require special attention and follow-up. The reasons for the racial disparity in the development of CAA, particularly among Hispanic children, should be further investigated to devise more effective methods to reduce the risk of CAA.

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REFERENCES

1. Kawasaki T. Pediatric acute febrile mucocutaneous lymph node syndrome with characteristic desquamation of fingers and toes: my clinical observation of fifty cases. *Pediatr Infect Dis J*. 2002;21:1–38.
2. Rowley AH, Shulman ST. Kawasaki syndrome. *Clin Microbiol Rev*. 1998;11:405–414.
3. Mason WH, Takahashi M. Kawasaki syndrome. *Clin Infect Dis*. 1999; 28:169–87.
4. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet*. 2004;364:533–544.
5. Belay ED, Holman RC, Clarke MJ, et al. The incidence of Kawasaki syndrome in West Coast health maintenance organizations. *Pediatr Infect Dis J*. 2000;19:828–832.
6. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics*. 2003;112:495–501.
7. Holman RC, Curns AT, Belay ED, et al. Kawasaki syndrome in Hawaii. *Pediatr Infect Dis J*. 2005;24:429–433.
8. Yanagawa H, Nakamura Y, Yashiro M, et al. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. *Pediatrics*. 2001;107:e33. Available at: http://www.pediatrics.org/cgi/content/full/107/3/e33.
9. Du ZD, Zhang T, Liang L, et al. Epidemiologic picture of Kawasaki disease in Beijing from 1995 through 1999. *Pediatr Infect Dis J*. 2002;21:103–107.
10. Newburger JW, Taubert KA, Shulman ST, et al. Summary and abstracts of the Seventh International Kawasaki Disease Symposium: December 4–7, 2001, Hakone, Japan. *Pediatr Res*. 2003;53:153–157.
11. Chang LY, Chang IS, Lu CY, et al. Epidemiologic features of Kawasaki disease in Taiwan, 1996–2002. *Pediatrics*. 2004;114:e678–e682. Available at: http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-0726.
12. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004;110:2747–2771.
13. Khan AS, Holman RC, Clarke MJ, Vernon LL, Gyurik TP, Schonberger LB. Kawasaki syndrome surveillance, United States, 1991–1993. In: Kato H, ed. *Kawasaki Disease.* Amsterdam, the Netherlands: Elsevier; 1995:80–84.
14. Gibbons RV, Parashar UD, Holman RC, et al. An evaluation of hospitalizations for Kawasaki syndrome in Georgia. *Arch Pediatr Adolesc Med*. 2002;156:492–496.
15. Kleinbaum D, Kupper L, Muller K, Nizam A. *Applied Regression Analysis and Other Multivariable Methods*. Pacific Grove, CA: Duxbury Press; 1998.
16. U.S. Census Bureau. United States Census 2000. Available at: http://www.census.gov/main/www/cen2000.html. Accessed June 10, 2005.
17. Rauch AM. Kawasaki syndrome: issues in etiology and treatment. *Adv Pediatr Infect Dis*. 1989;4:163–182.
18. Park YW, Park IS, Kim CH, et al. Epidemiologic study of Kawasaki disease in Korea, 1997–1999: comparison with previous studies during 1991–1996. *J Korean Med Sci*. 2002;17:453–456.
19. de Zorzi A, Colan SD, Guavreau K, Baker A, Sundel R, Newburger J. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. *J Pediatr*. 1998;133:254–258.
20. Jiao F, Yang L, Li Y, et al. Epidemiologic and clinical characteristics of Kawasaki disease in Shaanxi Province, China, 1993–1997. *J Trop Pediatr*. 2001;47:54–56.
21. Burns JC, Cayan DR, Tong G, et al. Seasonality and temporal clustering of Kawasaki syndrome. *Epidemiology*. 2005;16:220–225.