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Recurrent Kawasaki disease, United States and Japan

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Abstract

Background—Descriptive epidemiologic studies of recurrent and non-recurrent Kawasaki disease (KD) may identify other potentially important differences between these illnesses.

Methods—Data from the United States and Japan, the Centers for Disease Control and Prevention (CDC) national KD surveillance (1984–2008) and the 17th Japanese nationwide survey (2001–2002), respectively, were analyzed to examine recurrent KD patients <18 years of age meeting the CDC KD case or atypical KD case definition. These patients were compared to non-recurrent KD patients.

Results—Of the 5557 US KD patients <18 years of age during 1984–2008, 97 (1.7%) were identified as having had recurrent KD. Among the US Asian/Pacific Islander KD patients, 3.5% had recurrent KD, which was similar to the percentage identified among KD patients (3.5%) in the Japanese survey. Compared to non-recurrent KD patients, KD patients experiencing a recurrent KD episode were more likely to be older, fulfill the atypical KD case definition, and have coronary artery abnormalities (CAA) despite IVIG treatment.

Conclusions—Differences in the age, race, and frequency of CAA exist between recurrent and non-recurrent KD patients. The increased association of CAA with recurrent KD suggests that more aggressive treatment strategies in conjunction with IVIG may be indicated for the second episode of KD.

Keywords

Epidemiology Kawasaki disease; Kawasaki syndrome; mucocutaneous lymph node syndrome; recurrence

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Introduction

Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology that occurs worldwide.[1–7] KD primarily affects young children, with the majority of KD cases being <5 years of age, and it is more common in males and among children of Asian descent.[1–4,7–14] Japan has reported the highest incidence of KD, with 239.6 cases per 100,000 children <5 years of age reported for 2010.[7] In the United States (US), studies have shown incidence and hospitalization rates to range from approximately 9–21 cases per 100,000 children <5 years of age.[1, 3, 9, 11] In Hawaii, where a large proportion of children are of Asian descent, KD incidence has been reported to be 50.4 per 100,000 children <5 years of age, with an incidence of 210.5 for those of Japanese ancestry.[15]

KD causes significant morbidity in most patients and may result in cardiac and non-cardiac complications, the most serious of which are coronary artery abnormalities (CAAs).[1–4, 7–9] Treatment with intravenous immunoglobulin (IVIG) and aspirin is generally effective in reducing the occurrence of CAAs, and current recommendations in the United States specify that IVIG should be administered as soon as possible after illness onset.[2, 4] While no specific agent has been identified, features of KD appear to be consistent with an infectious etiology.[1, 2, 4, 16, 17] The lack of a diagnostic test for KD means that diagnosis is dependent upon an assessment of the presence of specific disease criteria using a case definition. Because IVIG therapy is believed to be more effective when administered early, physicians may choose to diagnose a patient with KD and begin treatment even if the KD case definition is not fulfilled.[4, 18, 19]

Previous studies in the United States and Japan have determined KD to recur in ~2–4% of patients.[2, 4, 7, 14, 16, 17, 20, 21] A study of KD patients in China reported that children with recurrent KD were more likely to present with incomplete clinical signs,[22] while Japanese studies have suggested that patients with recurrent KD may present with a more serious illness than the initial episode.[21. 23] Other Japanese studies have reported that recurrence is more common among children who were <3 years of age at the initial episode.[17, 20] In the United States, studies of recurrent KD have typically focused on a very small number of cases or have been limited to a single institution.[24] The present study includes the first in-depth analyses of KD recurrence using national Centers for Disease Control and Prevention (CDC) surveillance data. It also includes the first analyses of KD recurrence using CDC clinical KD case definitions applied to national KD survey data from Japan.

The goal of this study was to describe the epidemiology of recurrent KD among children in the United States and in Japan, and compare the KD patients with recurrence with non-recurrent KD patients by demographic factors, timing of treatment, and the occurrence of CAAs. Determining risk factors for KD recurrence may assist the treating physician, especially if earlier or more aggressive treatment for these cases is warranted.

Methods

United States data

Since 1976, CDC has conducted passive national surveillance for KD using a standardized KD case report form.[2, 8] Information from these forms has been entered into an electronic database beginning in 1984. The case report form has been periodically revised, most recently in 2004, and collects information on KD patient demographics, clinical signs, treatment, and complications.[25] In 1991, a separate question was added to the form to ascertain whether the KD case was recurrent and, if so, the onset date of the previous episode. Earlier versions of the form included recurrence as a possible response to disease outcome. In both scenarios, the classification of a KD case as recurrent has been dependent on the physician's assessment.

Records for children <18 years of age meeting the CDC epidemiologic case definition for KD or atypical KD with onset during 1984–2008 were selected for analysis.[2, 8] The CDC KD case definition requires that a patient has fever for ≥5 days (or fever until IVIG administration if given before the fifth day of fever) and the presence of at least 4 of the following 5 clinical signs: bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash, and cervical lymphadenopathy (at least 1.5 cm in diameter).[2, 8] Patients not meeting the KD case definition, but with fever of any duration and CAAs, are classified as having atypical KD.[2, 9] CAA is defined as the presence of coronary artery dilatation or aneurysm. When available, original hardcopies of report forms for recurrent cases were reviewed to ascertain the presence of KD recurrence. In instances where additional information on the form suggested that the recurrent admission was a continuation of the initial episode and not a true recurrence, the patient information was recoded as non-recurrent. Attempts were made to locate information in the database for the initial KD episode of each recurrent KD case; however, unless stated otherwise, analyses of recurrent KD cases used data obtained from the recurrent KD episode for comparison to non-recurrent KD cases.

Japan data

Nationwide surveys for KD have been conducted every two years since 1970.[6, 7, 12–14, 17, 26] Pediatricians from all pediatric hospitals and all other general hospitals with a pediatric department and ≥100 beds in Japan are asked to complete a questionnaire for each KD case they diagnose during the specified time period.[6, 7, 12–14, 17, 26] Questionnaires vary from survey to survey, but they typically include questions about demographics, treatment, complications, and recurrence. Data from the 17th Japanese national KD survey, covering the years 2001–2002, were obtained and translated to English by Dr. Ritei Uehara. This survey was sent to 2413 hospitals in Japan, with 68% responding.[26] The 17th survey is unique among the Japanese KD surveys in that information on KD clinical criteria was collected, allowing for analyses using the CDC KD case definition, which varies slightly from the Japanese KD case definition.[26] The Japanese KD definition does not require the presence of fever, but includes it as 1 of 6 criteria along with the 5 CDC KD criteria mentioned previously. Cases meeting 5 or 6 criteria are considered complete cases; those with 4 criteria and CAAs are classified as incomplete KD.[26] While the US KD definition

specifies a size (≥1.5 cm) for cervical lymphadenopathy, the Japanese definition does not; size information was not available in the Japanese survey, so patients recorded as having cervical lymphadenopathy in the Japanese data were classified as meeting this criterion for the purposes of applying the US CDC KD case definition. KD cases in the Japanese survey are classified as recurrent if there is an interval of at least two months from the onset of the first KD illness to onset of the new episode.[17]

Statistical Analysis

The Wilcoxon rank-sum test was used for comparison of continuous variables such as patient age. The Chi-square test and Fisher's exact test (two-sided) were used, as appropriate, to compare categorical variables including the presence of clinical criteria, treatment with IVIG before the fifth day of illness, and the occurrence of CAAs. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to compare KD recurrence by race and ethnicity. Statistical analyses were performed using SAS version 9.2 (SAS institute, Cary, NC). A p-value <0.05 was considered as the significance level.

Results

United States

There were 9636 KD patients <18 years of age reported to the US CDC KD surveillance program with onset during 1984–2008, with 6195 (64.3%) having recurrence data available. A majority (97.8%) of these 6195 patients had KD onset after 1990. Of the 6195 patients, 5339 (86.2%) met the CDC KD case definition, 218 (3.5%) met the atypical KD case definition, and 638 (10.3%) did not meet either case definition. The 5557 patients with recurrence data meeting either the CDC KD case definition or atypical KD case definition resided in 48 states and the District of Columbia, with 43.1% of the patients living in California. KD recurrence was indicated for 97 of the 5557 patients (1.7%), with a significantly higher percentage of recurrent cases being found among atypical KD patients compared to those meeting the CDC KD case definition (9 of 218 (4.1%) and 88 of 5339 (1.6%) patients, respectively) (p=0.006). Eleven of the 638 (1.7%) KD patients not meeting the CDC KD case definition or atypical KD case definition were recurrent; this proportion was not significantly different to the proportion of recurrence among KD patients meeting the CDC KD case definition or atypical KD case definition.

The annual percentage of recurrent cases among patients meeting the CDC KD case definition and atypical KD case definition was relatively stable, ranging from 0.4%–2.7% during the 1991–2008 period when most recurrence data were available. The percentages of recurrent KD cases among male and female KD patients (1.9% and 1.3%, respectively) were not significantly different (p=0.07). The 48 recurrent KD patients for whom age information was available for the initial KD episode had a median age of 21.5 months (mean 26.1, range 3–68 months), which was significantly younger than non-recurrent KD patients, who had a median age of 31 months (mean 39.1 months, range 0–214 months) (p=0.004). Recurrent KD patients at their recurrent KD episode, with a median age of 43 months (mean 47 months, range 3–148 months), were significantly older than the non-recurrent KD patients (p=0.002). For 48 recurrent KD patients with information available on the time between KD

episodes, the median duration was 17 months (mean 22.5 months, range 2–140 months). No recurrent KD patients were reported to have died; three deaths (0.05%) were reported among non-recurrent KD patients. For KD patients meeting the CDC KD case definition (atypical KD cases excluded), there were no significant differences in the presence of clinical criteria for recurrent and non-recurrent cases (Table 1).

For recurrent KD patients with treatment information available, most (71 of 74, 96.0%) received IVIG; if given IVIG, recurrent KD patients were more likely to receive treatment before the 5th day of illness compared to non-recurrent KD patients (44.6% vs. 29.9%, p=0.01). Of the 79 recurrent patients meeting the CDC KD case definition who had CAA information available, 19 (24.1%) had CAAs, which was significantly more than the 14.3% of non-recurrent KD patients with CAAs (p=0.01) (Table 1). All recurrent patients meeting the CDC KD case definition with CAAs with treatment information available (n=14) received IVIG; 45.5% (5 of 11) received treatment within 5 days of onset. Among recurrent KD patients with atypical KD, who by definition had CAAs, 5 of 8 (62.5%) received IVIG, and 33.3% (1 of 3) received the treatment within 5 days.

Previous admission data were available for 11 recurrent KD patients (Table 2). Ten of 11 (90.9%) met the CDC KD case definition on their initial KD episode. Eight of these 10 (80.0%) met the CDC KD case definition on their recurrent KD episode; the remaining 2 met criteria for atypical KD. Three of 10 (30.0%) patients with CAA information available had CAAs on their initial KD episode.

The proportion of Asian US KD patients that were recurrent was higher compared to that for white KD patients (3.5% and 1.5%, respectively; RR 2.3, 95% CI 1.4, 3.7) (Table 3). There was no difference in the percentage of recurrent KD patients between Asian male and Asian female KD patients (4.1% and 2.6%, respectively, p=0.26). The median age for Asian recurrent KD patients was 47 months (mean 47.2 months, range 5–141 months), which was similar to the median age of 43 months for white recurrent KD patients and significantly older than the median age of 28 months (mean 33.5, range 1–188) for Asian non-recurrent cases (p<0.001). All Asian recurrent KD patients with treatment information available (n=28) received IVIG; Asian recurrent KD patients were more likely to receive treatment before the 5th day of illness compared to non-recurrent Asian KD patients who received treatment (p=0.01). Of the 25 Asian recurrent KD patients meeting the CDC KD case definition and with CAA information available, 5 (20.0%) had CAAs, which was not significantly different compared to the 18.6% of Asian non-recurrent KD patients with CAAs (p=0.86). Four of the 5 patients had information reported about the start of treatment; all 4 received IVIG within 5 days.

Japan

There were 16949 physician-diagnosed KD patients <18 years of age with recurrence data available reported in the 17th national KD survey. Of these, 13240 (78.1%) met the CDC KD case definition, 634 (3.7%) met the atypical KD definition, and 3075 (18.1%) did not meet either definition. Of the 13874 patients meeting the CDC KD case definition or atypical KD case definition, 483 (3.5%) were recorded as having recurrent KD; a significantly higher percentage of recurrent cases were found among atypical KD patients

compared to those meeting the CDC KD case definition (34 of 634 (5.4%) and 449 of 13240 (3.4%) patients, respectively) (p=0.01). There was no difference in the percentage of recurrent cases between male and female patients (3.6% and 3.3%, respectively, p=0.38). Fewer recurrent KD patients meeting the US CDC KD case definition (atypical KD cases excluded) had rash compared to non-recurrent KD patients, while more recurrent KD patients had cervical lymphadenopathy (Table 1). The median age for recurrent KD patients was 42 months (mean 45.8 months, range 3.9–189.0 months), significantly higher than the 24.1 months for non-recurrent patients (mean 30.4 months, range 0.3–212.6 months) (p<0.0001). Most recurrent KD patients (447 of 483, 92.6%) received IVIG; if given IVIG, recurrent KD patients were not significantly more likely to receive treatment before the 5th day of illness compared to non-recurrent KD patients (p=0.07). Of recurrent KD patients meeting the CDC KD case definition with CAA information available, 86 of 449 (19.2%) had CAAs, significantly more than the 1802 of 12791 (14.1%) non-recurrent KD patients with CAAs (p=0.003). Almost all recurrent KD patients meeting the CDC KD case definition with CAAs had IVIG treatment (85/86, 98.8%); 37.8% (31 of 82) received treatment within 5 days. Among recurrent KD patients with atypical KD and CAAs, 29 of 34 (85.3%) received IVIG, and 21.4% (6 of 28) received the treatment within 5 days.

Discussion

Consistent with previous studies, KD recurrence was reported in a small percentage of KD cases.[2, 4, 7, 14, 16, 17, 20, 21] Patients with recurrent KD tended to be older than KD patients without recurrence, which was expected given that they had experienced a previous episode of KD. Asian children in the United States were at increased risk of KD recurrence compared to white KD patients. Despite the heterogeneity of the Asian race classification in the United States, which includes various Asian populations as well as Pacific Islanders, recurrence among Asian children with KD (3.5%) was remarkably similar to recurrence among Japanese children with KD in Japan (3.5%). In the United States and Japan, recurrent KD patients overall were more likely to have CAAs compared to non-recurrent KD patients; for US Asian KD patients alone, a significant difference was not found, which could be influenced by the smaller numbers available for analysis.

The difference in CAA occurrence between recurrent and non-recurrent US KD cases is particularly notable because recurrent KD patients, possibly resulting from increased suspicion of KD by doctors aware of a previous KD episode, were more likely to receive IVIG before the fifth day of illness. While only 11 patients in the US CDC database had matched information for initial and recurrent KD episodes, the following findings from these episodes were consistent with previous studies:[17, 21] CAAs were more commonly reported in recurrent cases that also had CAA at the initial episode, most patients were <3 years of age at their initial episode, and the majority of patients had recurrence within two years of their initial episode.

Limitations of the study included the inability to verify KD recurrence for many reported recurrent KD patients in the US CDC database. Dates of the initial KD episode were not available for 53% of the US recurrent KD patients, and it is possible that some patients may have been classified as recurrent when they were actually experiencing a continuation of the

initial episode. Conversely, some recurrent KD patients may not have been identified as recurrent if the person completing the form was not aware of the previous KD episode or if the initial or recurrent illness had an atypical presentation. The US CDC database has limited availability of recurrence data prior to 1991, and the CDC KD surveillance system is passive.[2] Some states and medical centers do not report or fully report KD cases, while other states, notably California, are more represented in the database. For the Japanese national database, it has been reported that the majority of KD patients are identified through the national KD surveys, with more than 90% of KD patients treated in surveyed hospitals.[12]

Further study of well-defined recurrent KD patients, particularly focusing on the initial KD episode, the treatment or treatments administered, and treatment response, is needed to better understand KD recurrence and to appropriately treat such patients. Despite the finding that US children with recurrent KD are more likely to be treated before the fifth day of illness, recurrent KD patients remain at increased risk of CAAs compared to non-recurrent KD cases. A study using Japanese data has also reported that IVIG nonresponse may be more likely when treating recurrent episodes of KD.[6] These findings indicate that a different treatment strategy, such as inclusion of a more potent anti-inflammatory drug with the initial IVIG treatment, may be warranted in patients showing early signs of KD recurrence. Kobayashi et al. recently reported that the use of steroids was effective in reducing the occurrence of CAAs among severe KD patients in Japan.[27]

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Table 1

Recurrent Kawasaki disease (KD) and non-recurrent KD patients <18 years of age meeting the CDC KD case definition by criterion and coronary artery abnormality (CAA) status, United States (1984–2008) and Japan (2001–2002)*

Criterion/CAA status	Recurrent KD Number (%)		Non-recurrent KD Number (%)		P-value**	
	USA	Japan	USA	Japan	USA	Japan
Bilateral conjunctival injection	86/88 (97.7)	432/449 (96.2)	5067/5203 (97.4)	12391/12791 (96.9)	1.00	0.43
Oral mucosal changes	86/86 (100.0)	429/449 (95.6)	5165/5239 (98.6)	12231/12791 (95.6)	0.63	0.94
Peripheral extremity changes	81/86 (94.2)	398/449 (88.6)	4786/5150 (92.9)	11598/12791 (90.7)	0.65	0.15
Rash	85/88 (96.6)	411/449 (91.5)	5110/5221 (97.9)	12020/12791 (94.0)	0.44	0.03
Cervical lymphadenopathy§	52/82 (63.4)	388/449 (86.4)	2920/4787 (61.0)	9525/12791 (74.5)	0.66	<0.001
Coronary artery abnormality	19/79 (24.1)	86/449 (19.2)	698/4890 (14.3)	1802/12791 (14.1)	0.01	0.003

* US data from Centers for Disease Control and Prevention (CDC) KD surveillance, 1984–2008; Japanese data from 17th nationwide survey, 2001–2002

** Chi square test or Fisher's exact test (two-sided), as appropriate, comparing recurrent KD cases to non-recurrent KD cases

§ Cervical lymphadenopathy ≥1.5 cm in USA, no size requirement in Japan

Table 2

Initial and recurrent Kawasaki disease (KD) episodes for recurrent KD patients <18 years of age, United States, 1984–2008*

Patient demographics	Initial			Recurrent			
	Criteria present	CAA	Dx	Criteria present	CAA	Dx	Time between episodes(m)
27 m, black, non-Hispanic female	5/5	No	KD	5/5	Unk	KD	3
29 m, white, Hispanic Male	5/5	No	KD	5/5	No	KD	12
44 m, black, non-Hispanic male	4/5	No	KD	5/5	No	KD	50
40 m, Asian, non-Hispanic female	4/5	No	KD	5/5	No	KD	16
8 m, Asian, non-Hispanic female	4/5	Unk	KD	4/5	Unk	KD	35
32 m, Asian, non-Hispanic male	4/5	Yes	KD	5/5	No	KD	36
63 m, white, non-Hispanic male	4/5	No	KD	4/5	No	KD	16
5 m, white, non-Hispanic male	4/5	No	KD	0/5	Yes	A. KD	18
32 m, white, non-Hispanic male	3/5	No	X	4/5	No	KD	27
27 m, black, non-Hispanic male	4/5	Yes	KD	5/5	Yes	KD	11
21 m, white, Hispanic female	4/5	Yes	KD	3/5	Yes	A. KD	2

*CAA=coronary artery abnormality, Dx=diagnosis, m=months, Unk=unknown, A. KD=atypical KD, X=did not meet the Centers for Disease Control and Prevention case definition for KD or atypical KD but was diagnosed as KD by physician

Table 3

Recurrent Kawasaki disease (KD) patients <18 years of age by race and ethnicity, United States, 1984–2008*

	Recurrent KD	Non-recurrent KD	Recurrence (%)	RR, 95% CI
Race**	**n=90**	**n=4908**		
White	46 (51.1%)	2926 (59.6%)	46/2972 (1.5%)	Reference
Black	12 (13.3%)	912 (18.6%)	12/924 (1.3%)	0.8 (0.4, 1.6)
Asian/Pacific Islander	29 (32.2%)	807 (16.4%)	29/836 (3.5%)	2.3 (1.4, 3.7)
American Indian/Alaska Native	0 (0.0%)	21 (0.4%)	0/21 (0.0%)	——
Other	3 (3.3%)	242 (4.9%)	3/245 (1.2%)	0.8 (0.2, 2.6)
Ethnicity**	**n=52**	**n=4342**		
Non-Hispanic	39 (75.0%)	3208 (73.9%)	39/3247 (1.2%)	Reference
Hispanic	13 (25.0%)	1134 (26.1%)	13/1147 (1.1%)	0.9 (0.5, 1.8)

* RR=risk ratio, CI=confidence interval

** 10.1% of patients missing race information, 20.9% of patients missing ethnicity information