Kawasaki Syndrome and Factors Associated With Coronary Artery Abnormalities in California

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**Background:** Kawasaki syndrome (KS) occurs in children <18 years of age and is the leading cause of acquired heart disease among children in the United States. Understanding the epidemiology of KS and factors associated with coronary artery abnormalities (CAA) may lead to timely diagnosis and treatment of KS and could limit CAA.

**Methods:** Epidemiologic characteristics, including risk factors for the development of CAA, among KS and incomplete KS patients <18 years of age with onset during 2000–2009 reported by the California Department of Public Health to the Centers for Disease Control and Prevention’s national KS surveillance system were analyzed.

**Results:** A total of 2056 KS and incomplete KS patients <18 years of age were reported during 2000–2009. The median age of patients was 2 years; 60% of patients were male. Of 1818 patients with race information reported, 56% were white and 28% were Asian/Pacific Islander. Ninety-eight percent of patients received intravenous immunoglobulin. Of 1843 patients with information on cardiac complications, 89 (5%) had coronary artery aneurysms and 341 (19%) had CAA. Characteristics associated with the occurrence of CAA in KS patients were male sex, Asian/Pacific Islander race, age <1 year or 9–17 years, and not receiving intravenous immunoglobulin treatment before the fifth day of illness.

**Conclusions:** This study suggests that intravenous immunoglobulin treatment before the fifth day of illness may reduce CAA among KS patients. Timely diagnosis and treatment of KS continue to be important in reducing the occurrence of cardiac complications.

**Key Words:** Kawasaki syndrome, children, epidemiology, coronary artery abnormalities, California

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**MATERIALS AND METHODS**

The CDPH maintained a mandatory, passive reporting surveillance system for KS during the study period 2000–2009. Health-care providers were mandated to report cases of KS to their local health departments, who, in turn, reported these cases to the CDPH. Data reported from the CDPH to the CDC’s national KS surveillance system were used for this study. The CDC has conducted passive national KS surveillance since 1976; data collected include demographics, clinical outcomes, symptoms,
Kawasaki Syndrome

The CDC KS case definition was used to define KS and incomplete KS cases. A reported KS case met the CDC case definition if the patient had either fever for ≥5 days or fever until the date of IVIG treatment if treatment was given before the fifth day of illness and had at least 4 of the following 5 symptoms: bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash and cervical lymphadenopathy (at least 1 lymph node ≥1.5 cm in diameter). A patient with any length of fever and CAA, and who did not meet the CDC KS case definition, was classified as a case of incomplete KS. CAA was defined as the presence of coronary artery dilatation (CAD) or coronary artery aneurysm as reported on the case report form.

Demographic characteristics, symptoms and outcomes and whether IVIG treatment was administered before the fifth day of illness were analyzed for all KS patients. Race groups were collected as white, black, Asian/Pacific Islander, American Indian/Alaska Native and other; 12% of patients were missing race information. American Indians/Alaska Natives were included with the “other” race group because of the small number of patients for detailed analyses. Sixteen percent of KS patients were missing ethnicity information.

Analyses assessing risk factors for CAA were limited to patients who had information available on cardiac complications [90% (1843/2056)]. To evaluate the potential effect of incomplete KS cases, separate analyses including and excluding incomplete KS cases were conducted. Univariate analysis was conducted to identify which predictor variables would be included in the multivariate analysis. After assessing confounding and collinearity, all significant predictor variables (P < 0.1) and interaction terms were included in the initial multiple logistic regression model. The predictor variables used in the model included race, sex, age and IVIG treatment started before the fifth day of illness. Adjusted odds ratios and 95% confidence intervals were calculated from multiple logistic regression models using hierarchical backward elimination, which tested for associations between predictor variables and the occurrence of CAA. Statistical analyses were conducted using SAS v. 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

During 2000–2009, a total of 2206 patients <18 years of age with physician-diagnosed KS, as indicated by a completed KS case report form, were reported to the CDPH. Of these, 2056 (93%) patients met the CDC case definition for KS or incomplete KS (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B217). Among these patients, 42 (2%) were incomplete KS cases and 29 (1.4%) were reported as recurrent cases. The KS cases were reported by 47 of 58 counties; the majority of the KS cases were reported from the 3 most populous counties of Los Angeles (26%), San Diego (25%) and Orange (10%). Most (82%) patients were <5 years of age. Incomplete KS patients had a younger median age (1 year; quartiles: 0, 2) than typical KS patients (2 years; quartiles: 1, 4; P < 0.005); there were no patients aged 16–17 years (Fig. 1). Sixty percent of patients were male (see Table, Supplemental

FIGURE 1. The age distribution of Kawasaki syndrome (KS) and incomplete KS cases <18 years of age, California, 2000–2009.
Of 1818 patients with race reported, 56% were white, 7% were black, 28% were Asian/Pacific Islander and 9% were other or American Indian/Alaska Native race (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B217). Forty-six percent of patients with ethnicity reported were of Hispanic/Latino ethnicity.

The highest proportion of onset of KS cases occurred during January through April (43%) with a peak in March (Fig. 2). The median length of hospitalization was 3 days (quartiles: 2, 4; see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B218). Of 1555 patients with length of fever reported in days, the median fever duration was 6 days (quartiles: 5, 7).

Ninety percent of KS patients had fever for ≥5 days. The most common symptom was oral mucosal changes (98%). The least commonly reported sign or symptom was cervical lymphadenopathy (52%); infants (<1 year of age) were the least likely to have this sign reported (28%). Almost all patients (98%) received IVIG treatment; 26% were treated with IVIG before the fifth day of illness while still febrile.

Four deaths, all among children <6 years of age, were reported; no deaths were reported for children with the onset after 2004. Three of the 4 decedents were tested for the presence of cardiovascular complications, and all had aneurysms. Three of the 4 children who died were white; all 3 decedents with sex reported were female.

Of the total KS cases, 1843 (90%) had information on cardiac complications. Of these, 341 (19%) had CAA (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B218). Of the patients with CAA, 87% were <5 years of age and 82% had CAD. Coronary artery aneurysms were found in 5% of patients (89/1843). Both infants and children 9–17 years of age with KS had a higher proportion of CAA (30% and 26%, respectively) than patients 1–8 years of age (16%, P < 0.0001; Table 1). Males had a higher proportion of CAA than females (22% versus 14%, respectively; P < 0.0001), and patients reported as Asian/Pacific Islander race had a higher proportion of CAA than all other race groups (23%; Table 1). Hispanic and non-Hispanic KS patients had similar proportions of CAA (20% and 19% respectively, P = 0.5). Patients without CAA were more likely to have had IVIG started before the fifth day of illness compared to patients with CAA (27% versus 19%; P = 0.002).

Male sex, age <1 year or 9–17 years of age, Asian/Pacific Islander race and those not receiving IVIG treatment before the fifth day of illness were identified as risk factors for the development of CAA (Table 1). Infants and males were about 2 times more likely to develop CAA than children 1–8 years of age and females, respectively. Children 9–17 years of age were also at increased risk for CAA compared with children 1–8 years of age. Initiating IVIG treatment before the fifth day of illness while the patient was still febrile showed a protective effect for the development of CAA (adjusted odds ratio: 0.5; 95% confidence interval: 0.4–0.7). Multiple logistic regression analysis excluding incomplete KS cases resulted in similar effect estimates.

Other than CAA, mitral regurgitation (5%) and pericarditis or pericardial effusion (5%) were the most common cardiac complications reported in the KS cases. Arthralgia (3%) and meitis or sterile pyuria (3%) were the most common noncardiac complications among all reported patients. Among incomplete KS cases, 14% had mitral regurgitation and 17% had pericarditis or pericardial effusion.
**TABLE 1.** Characteristics Associated With Coronary Artery Abnormalities (CAA) Among Kawasaki Syndrome (KS) and Incomplete KS Cases <18 y of Age, California, 2000–2009*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CAA, N (%)</th>
<th>No CAA, N (%)</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>341 (18.5)</td>
<td>1502 (81.5)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>97 (29.9)</td>
<td>228 (70.2)</td>
<td>2.4 (1.8–3.2)</td>
</tr>
<tr>
<td>1–8</td>
<td>228 (15.7)</td>
<td>1228 (84.3)</td>
<td>Referent</td>
</tr>
<tr>
<td>9–17</td>
<td>16 (25.8)</td>
<td>46 (74.2)</td>
<td>2.0 (1.0–3.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>238 (21.5)</td>
<td>868 (78.5)</td>
<td>1.8 (1.4–2.4)</td>
</tr>
<tr>
<td>Female</td>
<td>100 (13.9)</td>
<td>619 (86.1)</td>
<td>Referent</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>160 (17.6)</td>
<td>750 (82.4)</td>
<td>Referent</td>
</tr>
<tr>
<td>Black</td>
<td>19 (16.0)</td>
<td>100 (84.0)</td>
<td>0.8 (0.5–1.4)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>106 (23.1)</td>
<td>352 (76.9)</td>
<td>1.4 (1.0–1.8)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (17.0)</td>
<td>127 (83.0)</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>IVIG started before fifth day of illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (14.1)</td>
<td>372 (85.9)</td>
<td>0.5 (0.4–0.7)</td>
</tr>
<tr>
<td>No</td>
<td>268 (21.1)</td>
<td>1005 (79.0)</td>
<td>Referent</td>
</tr>
</tbody>
</table>

*Only those patients who were tested for cardiovascular complications and received IVIG were included in the analysis.

**DISCUSSION**

Previous studies have used the CDC’s passive KS surveillance system to investigate the occurrence of KS in the United States. The present study focused on analyzing surveillance data from California primarily because KS was a reportable disease within the state during the study period, and California has a larger and more diverse population than other states. Collaboration between the CDC and the CDPH allowed for a more complete collection of case report forms.

Findings from this study were consistent with previous studies regarding the general KS epidemiology: children <5 years of age, children of Asian descent and males were more susceptible to KS. Patients who were reported as Asian/Pacific Islander race appeared overrepresented among the KS cases (28%) when compared with the estimated racial distribution of California’s population <18 years of age: 78% white, 8% black and 12% Asian/Pacific Islander. Of the KS patients with available ethnicity information, 45% were Hispanic/Latino ethnicity; this proportion would be expected based on California’s estimated proportion of children <18 years of age of Hispanic/Latino ethnicity (47%). The geographic distribution of KS cases in California reflected the population distribution; more patients were reported from counties with a larger population of children <18 years of age.

A notably small proportion of patients were reported with cervical lymphadenopathy (52%) compared with the other 4 case-defining physical findings (92–98%). Cervical lymphadenopathy is consistently the least reported clinical finding with proportions of patients with cervical lymphadenopathy ranging from 16% to 82% in previous studies. Because infants are less likely to have cervical lymphadenopathy reported or satisfy the size requirement (≥1.5 cm diameter), infants may be at risk for delayed diagnosis or treatment. Some researchers have suggested that the criteria for KS for infants be modified or relaxed.

A high proportion of patients experienced CAA (19%); this proportion was comparable with 13–19% of KS cases with CAA reported in recent studies. Most KS and incomplete KS cases with CAA had CAD (82%); this reflects findings from a recent study reporting that the majority of CAA are due to CAD, primarily attributed to enhanced CAD detection. Male sex, age <1 year or age 9–17 years, and Asian/Pacific Islander race were identified as risk factors for the development of CAA in KS cases, reflecting risk factors reported for CAA in previous studies.

It is recommended that treatment with IVIG be started within the first 10 days of illness or as soon as possible after a clinical diagnosis of KS is suspected, and delaying treatment can increase the risk of development of CAA. Several studies have examined if there is additional benefit of “early treatment” (within the first 5–7 days of illness), although no consensus has been reached on efficacy of early treatment. In the present study, treatment with IVIG before the fifth day of illness appeared to be protective against the development of CAD; however, our findings could not show if there is any additional benefit from treatment before the fifth day of illness compared with treatment before the 10th day of illness because of the inability to exclude patients treated after the 10th day of illness. The protective effect of treatment before the fifth day of illness found in this study may have been strengthened by the inclusion of those treated after the 10th day of illness in the “treated on or after the fifth day of illness” group.

There are limitations in the present study. There were variables with missing or incomplete data on some case reports; inaccuracies or missing information on the KS case report form could have precluded patients from meeting the CDC KS case definition and from being included in the analysis. In future studies, collection of the date of fever onset, illness onset, hospitalization, IVIG treatment, first and subsequent cardiac echocardiograms and date first afebrile after initiation of IVIG would be useful for data verification and more detailed analyses.

The findings from this study suggest that IVIG treatment of children with KS before the fifth day of illness may reduce CAA. Until the etiology of KS is known, understanding the epidemiology of KS and risk factors for CAA may help guide physicians to an earlier diagnosis and more timely treatment, which continue to be important in reducing potential cardiac complications. Although the CDC’s KS case definition is useful for epidemiological studies and surveillance, waiting to diagnose KS and initiate IVIG treatment until patients develop the complete manifestations of the disease may put some patients, particularly infants, at risk of developing KS complications. Physicians should increase their index of suspicion for KS diagnosis in patients who have prolonged unexplained fever with ≥2 clinical criteria and supportive laboratory data and consider prompt KS treatment regardless of a negative finding on cardiac echocardiogram.
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REFERENCES


