Hospitalizations for Kawasaki Disease Among Children in the United States, 1988–1997

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ABSTRACT. *Objective.* **To evaluate the epidemiologic pattern of Kawasaki disease (KD) in the United States over 10 years.**

Methods. **The National Inpatient Sample, a stratified national sample of >900 hospitals in 22 states of the United States, was used. Data on hospital discharges from 1988–1997 were analyzed. Patients <18 years of age with a discharge diagnosis of KD were identified.**

Results. **There were 6442 patients with KD admitted to 651 hospitals. Median age at hospital admission was 2 years. Peak incidence by year of age was 1 year old. Children <2 years old accounted for 36.6% of all cases; <5 years old, 75.6%; and <10 years old, 95.6%. The age distribution seems to be wider than reported from Japan. The incidence for children <5 years old was 8.1 per 100 000 people in 1988, and increased to 18.5 in 1997. There were 3905 males (60.6%) and 2537 females (39.4%), for a male-to-female ratio of 1.54. The incidences were higher in winter and spring (December to May) and dropped to a nadir between July and September. No apparent change in seasonal pattern was noted over 10 years. The South census region showed a seasonal change 2 to 3 months ahead of other regions. The overall in-hospital mortality rate was 0.17%. The mortality rate in children ≥10 years (1.4%) was significantly higher in than children <10 years (0.11%).**

Conclusions. **KD affects mainly children under 5 years of age, with a peak incidence in children 1 to 2 years of age. The incidence of KD was rising over the study period. There is a male predominance. Although KD occurs year-round, the lowest incidence is seen from July through September. Such seasonal variation did not change over the 10 years. Seasonal pattern may vary in different geographic regions. Mortality from KD is rare, although children ≥10 years are at higher risk.** *Pediatrics* **2002;109(6). URL: http://www.pediatrics.org/cgi/content/full/109/6/e87;** ***Kawasaki disease, epidemiology, United States.***

ABBREVIATIONS. KD, Kawasaki disease; NIS, Nationwide Inpatient Sample; IVIG, intravenous immunoglobulin; AHA, American Heart Association.

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Kawasaki disease (KD) is an acute febrile illness of unknown cause.[1–3] It is known to affect young children causing persistent high fever and signs of systemic inflammation. KD is associated with development of coronary aneurysm and myocarditis and is the leading cause of acquired heart disease among children in the United States and many developed nations. Although KD is much more common in Japan, cases of KD have been reported worldwide. Epidemiologic studies have shown that KD affects mainly children under 5 years of age with a male predominance. Most epidemiologic information on KD has come from Japan where a nationwide epidemiologic survey is conducted every 2 years.[4–7] There has been limited, up-to-date epidemiologic information on KD in the United States.[8–12]

Recent reports indicate that most (>96%) children with KD are hospitalized.[13,14] Therefore, data from hospital discharges provide valuable sources for investigating the epidemiology of KD. This study used the largest inpatient care database in the United States—the Nationwide Inpatient Sample (NIS). The purpose of this study was to provide updated epidemiologic information on KD in the United States over a 10-year period, 1988–1997.

METHODS

Data Sources

This study used abstracted hospital discharge data from NIS. The NIS data are a stratified sample from the data derived from the Healthcare Cost and Utilization Project that represent 20% of all hospital discharges (including children's hospitals) of the United States. The Healthcare Cost and Utilization Project is a multistate database project maintained by the Agency for Healthcare Research and Quality. The number of states participating in the NIS data and the number of hospitals have increased over time. In 1988, the NIS data included 5.3 million hospital discharges from 759 hospitals in 8 states. In 1997, the number of discharges was 7.1 million from 1012 hospitals in 21 states.[15] States participating in the Healthcare Cost and Utilization Project are listed in Table 1.

The NIS data contain *International Classification of Diseases, Ninth Revision, Clinical Modification* discharge diagnosis and procedure codes assigned by hospitals in participating states to each individual discharge. The data include >100 clinical and nonclinical variables for each hospital stay, such as primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographics (eg, gender, age, race, median income for zip code), expected payment source, total charges, length of stay, and hospital characteristics. This study used 10 years of data (1988–1997) from NIS Release 1, 2, 3, 4, 5, and 6.

The demographic data on the child population of the United States were obtained from the 1980, 1990, and 2000 US Census, Department of Commerce, US Census Bureau. Child population

TABLE 1. Summary of Patients, Hospitals, and States Included in the Current Study From 1988 to 1997

Year	Number of Patients	Number of Hospitals	States Included
1988–1997	6442	651	AZ, CA, CO, CT, FL, GA, HI, IA, IL, KS, MA, MD, MO, NJ, NY, OR, PA, SC, TN, UT, WA, WI
1988	378	124	CA, CO, FL, IA, IL, MA, NJ, WA
1989	539	174	AZ, CA, CO, FL, IA, IL, MA, NJ, PA, WA, WI
1990	567	164	AZ, CA, CO, FL, IA, IL, MA, NJ, PA, WA, WI
1991	703	177	AZ, CA, CO, FL, IA, IL, MA, NJ, PA, WA, WI
1992	658	184	AZ, CA, CO, FL, IA, IL, MA, NJ, PA, WA, WI
1993	721	183	AZ, CA, CO, CT, FL, IA, IL, KS, MA, MD, NY, OR, PA, SC, WA
1994	662	188	AZ, CA, CO, CT, FL, IA, IL, KS, MA, MD, NJ, NY, OR, PA, SC, WA, WI
1995	605	185	AZ, CA, CO, CT, FL, IA, IL, KS, MA, MD, MO, NJ, NY, OR, PA, SC, TN, WA, WI
1996	719	188	AZ, CA, CO, CT, FL, IA, IL, KS, MA, MD, MO, NJ, NY, OR, PA, SC, TN, WA, WI
1997	890	210	AZ, CA, CT, FL, GA, HI, IA, IL, KS, MA, MD, MO, NJ, NY, OR, PA, SC, TN, UT, WA, WI

for each year of the study period was calculated by interpolating the census data.

Case Selection

For this study, pediatric patients (0 through 17 years of age) with a diagnosis code in the database indicating KD (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 446.1) were selected as the study population. Each patient in the database is assigned a unique sequence number, which allows identification of patients with multiple hospitalizations. For patients with multiple hospitalizations for KD, only the first hospitalization (determined by the month and year of hospitalization) was entered into the analysis.

To evaluate the geographic variation of KD epidemiology, the 22 states were grouped into 4 regions according to each state's census region designation. States in the West census region are Arizona, California, Colorado, Hawaii, Oregon, Utah, and Washington. States in the Midwest census region are Iowa, Illinois, Kansas, Missouri, and Wisconsin. States in the Northeast census region are Connecticut, Massachusetts, New Jersey, New York, and Pennsylvania. States in the South census region are Florida, Georgia, Maryland, South Carolina, and Tennessee.

Statistical Analysis

Descriptive continuous data, such as hospital charges and length of stay, are presented as mean ± standard deviation and median when appropriate. Continuous variables were compared using the Student t test. Categorical variables and proportions were compared using χ^2 test or Fisher exact test. A P value $<.05$ was considered statistically significant. Statistical analyses were performed using SPSS 8.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

A total of 6442 patients <18 years of age were admitted to 651 hospitals in 22 states over the 10-year study period. Table 1 lists the number of cases and hospitals from each year of the study period. The total number of cases in each hospital ranged from 1 to 297 cases. The highest number of average annual cases for a hospital was 50 cases per year. There were 890 cases of KD among children 0 to 17 years of age from the 1997 NIS data. Considering that NIS data represents 20% all hospital discharges in the United States, an estimated 4500 cases of KD occurred in the United States in 1997.

Age and Incidence

Median age at hospital admission was 2 years. Peak incidence by year of age was 1 year old (20.7% of all cases). Children <2 years old accounted for 36.6% of all cases, <5 years old accounted for 75.6%, and children <10 years old accounted for 95.6% cases (Fig 1).

The incidence of KD was calculated based on the 1990 US census data and the assumption that the NIS data represent 20% of all hospital discharges in the United States. For children <5 years of age, the incidence increased from 8.1 per 100 000 children <5 years old in 1988 to 18.5 in 1997. Figure 2 shows the incidence of KD over the 10-year study period. The incidence increased from 1988 to 1991, remained relatively unchanged till 1996, and rose again in 1997. The incidence for children <10 years old increased from 5.0 per 100 000 children <10 years old in 1988 to 11.7 in 1997. The pattern of incidence changes over time in children <10 years old, which was similar to that of children <5 years old as shown in Fig 2.

Gender

There were 3905 males (60.6%) and 2537 females (39.4%), for a male-to-female ratio of 1.54. As shown in Fig 3, the number of males exceeds the number of females in all ages. The male-to-female ratio for infants (<1 year) was 1.52, and the ratios for children <5 years and <10 years were the same at 1.50. The male-to-female ratio for children ≥10 years old was 3.0, which is significantly different from children <10 years old ($P < .01$). There was no significant geographic variation in the male-to-female ratio. The male-to-female ratio was 1.58 for West, 1.52 for Midwest, 1.55 for Northeast, and 1.53 for South. However, variation in male-to-female ratio was noted in different months of the year. The male-to-female ratio varied from 1.29 in January to 1.90 in November ($P < .01$).

Seasonal Variation

The 10-year study period was divided into two 5-year periods (1988–1992 and 1993–1997) to determine whether the seasonal pattern had changed over time. The 2 periods show similar seasonal pattern with lowest incidence in July through September (Fig 4). The incidences were higher in winter and spring (December to May). No apparent change in seasonal pattern of KD was noted over 10 years.

All 4 regions showed seasonal variation in the number of cases by month (Fig 5). In the South, the number of cases decreased in March and stayed low until October. In contrast, the number of cases in the West started to decrease in June, decreased further in July, and stayed low until December when it started to rise again. Northeast and Midwest showed seasonal patterns similar to that of the West. Therefore,

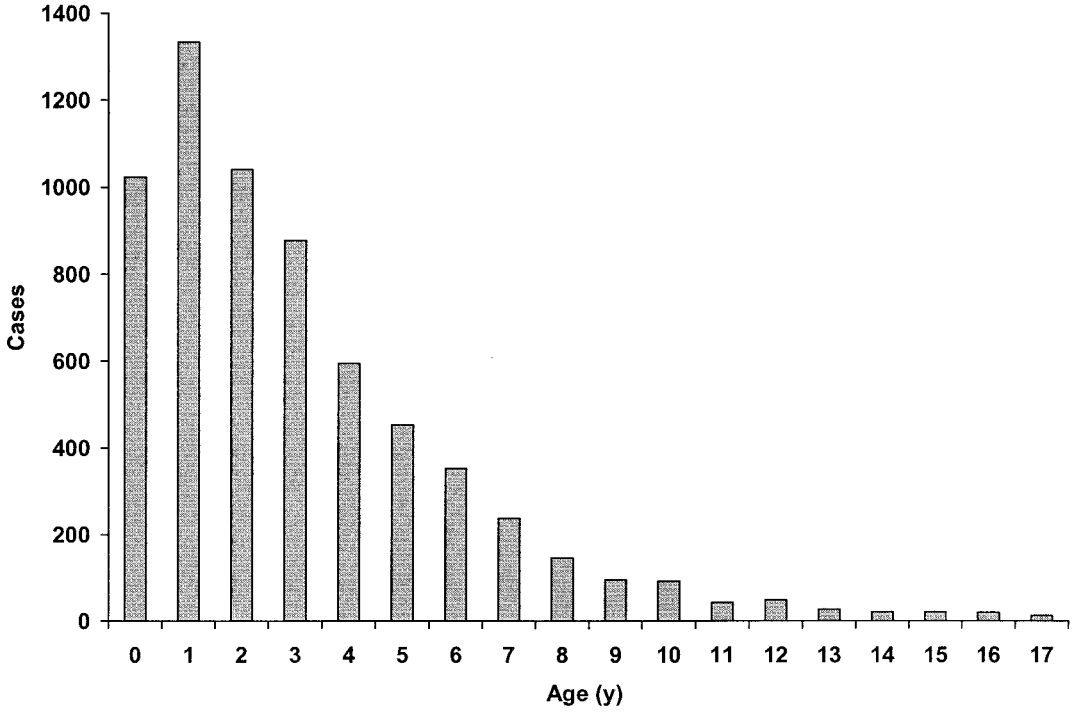

Fig 1. Number of cases in the NIS data presented by patients' age. The number of cases peaks at patients 1 to 2 years of age, followed by patients <1 year and 2 to 3 years of age, and then the number continues to decrease towards older age.

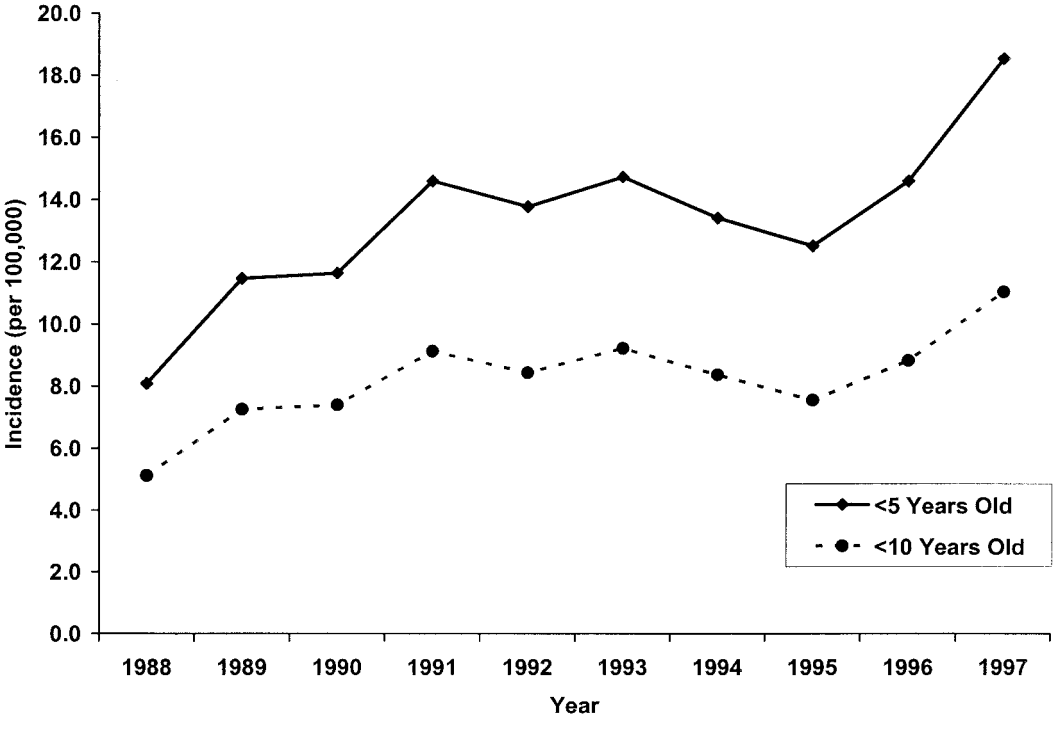

Fig 2. Incidence of KD in children <5 years and children <10 years over 1988–1997. Incidences are presented as cases per 100 000 children (<5 years and <10 years, respectively).

the South census region showed a seasonal change 2 to 3 months ahead of other regions.

Hospitalization and Outcomes

Of the days of the week when patients were admitted to the hospitals, the number of admissions was high on Monday (16.4% of all admissions), decreased on Tuesday (15.8%) and Wednesday (15.8%), decreased further on Thursday (15.0%), and rose again on Friday (16.9%). The number of admissions was lowest on weekends (Saturday 10.6% and Sunday 9.6%).

The overall median hospital length of stay was 3 days (mean 4.3 ± 4.8 days), ranging from 0 to 146 days. The median length of hospital stay decreased from 5 days in 1988 to 4 days in 1989 and to 3 days

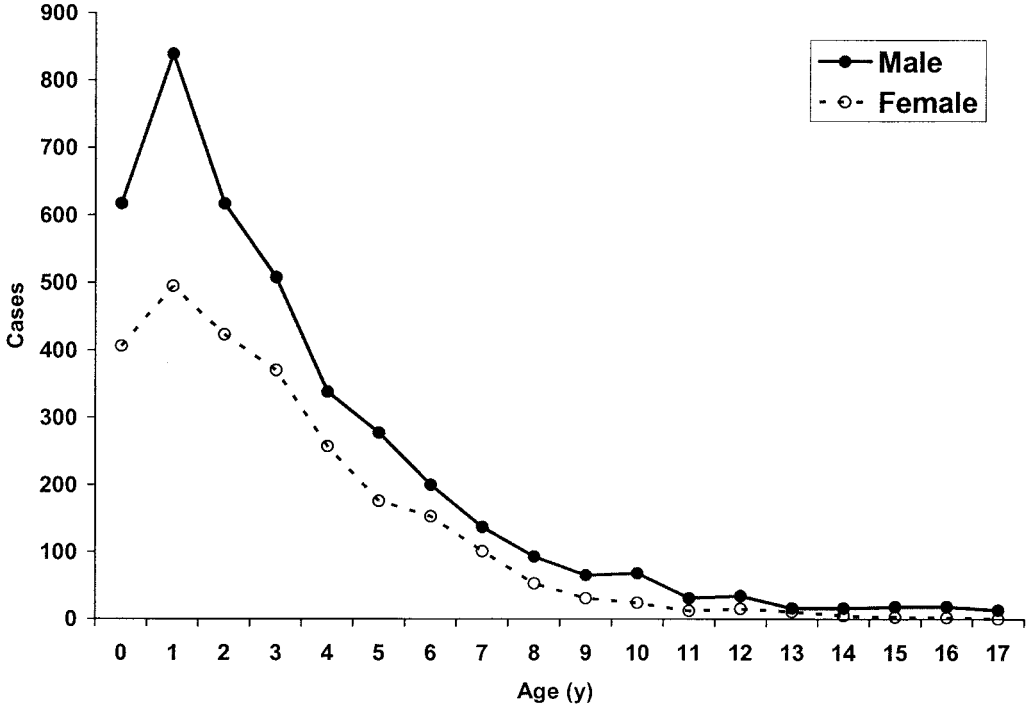

Fig 3. Comparing the number of cases between males and females from 0 to 17 years of age.

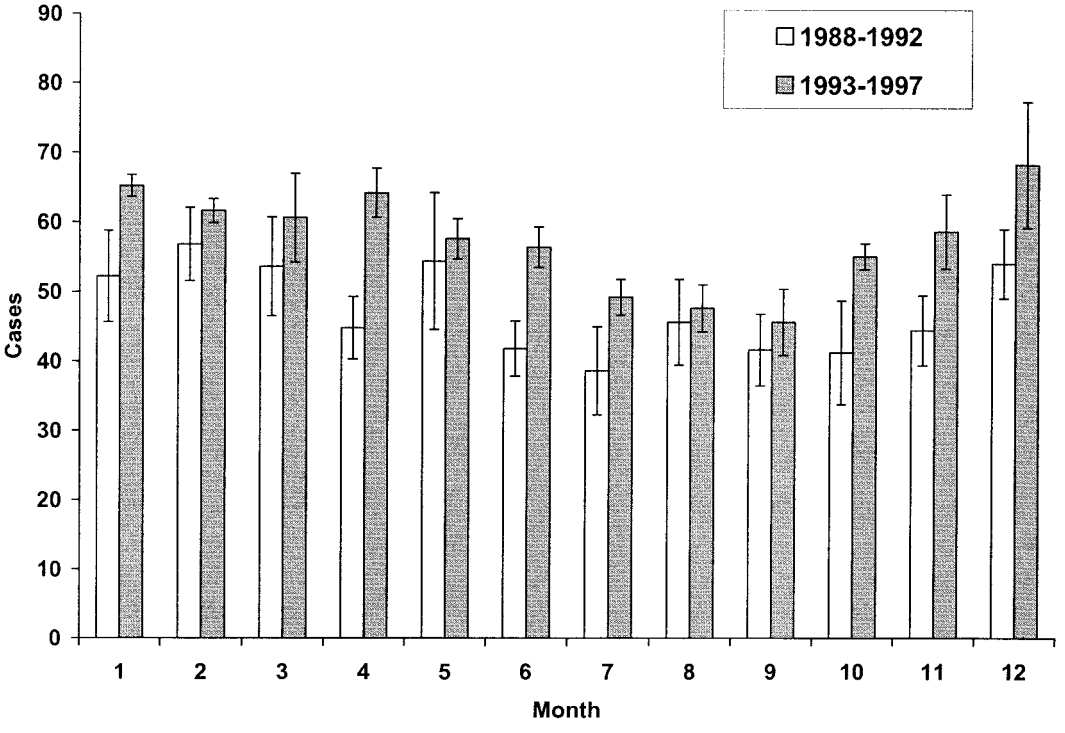

Fig 4. Seasonal changes of KD in the first period 1988–1992 and second period 1993–1997. The 2 periods showed similar seasonal variation. Vertical bars denote standard errors of the mean.

from 1990 to 1997. The median hospital charge was \$5652 (mean \$8025 ± 12 016), ranging from \$198 to \$426 060 (without adjustment for inflation rate over time).

There were 11 in-hospital deaths, yielding an overall mortality rate 0.17%. The deaths occurred from day 1 to day 24 of hospitalization. The majority of deaths (7) occurred in the first week of hospitalization. There were 2 deaths in infants (<1 year of age). The mortality rate of infants (0.20%) was not different from children >1 year of age (0.17%). Four deaths occurred in children ≥10 years old (all males), yielding a mortality rate of 1.40% in children 10 to 17 years old, which was significantly higher than mortality rate of 0.11% in children <10 years old ($P < .01$). The relative risk for mortality comparing children ≥10 years old with children <10 years old is 12.3. The causes of death in these cases could not be deter-

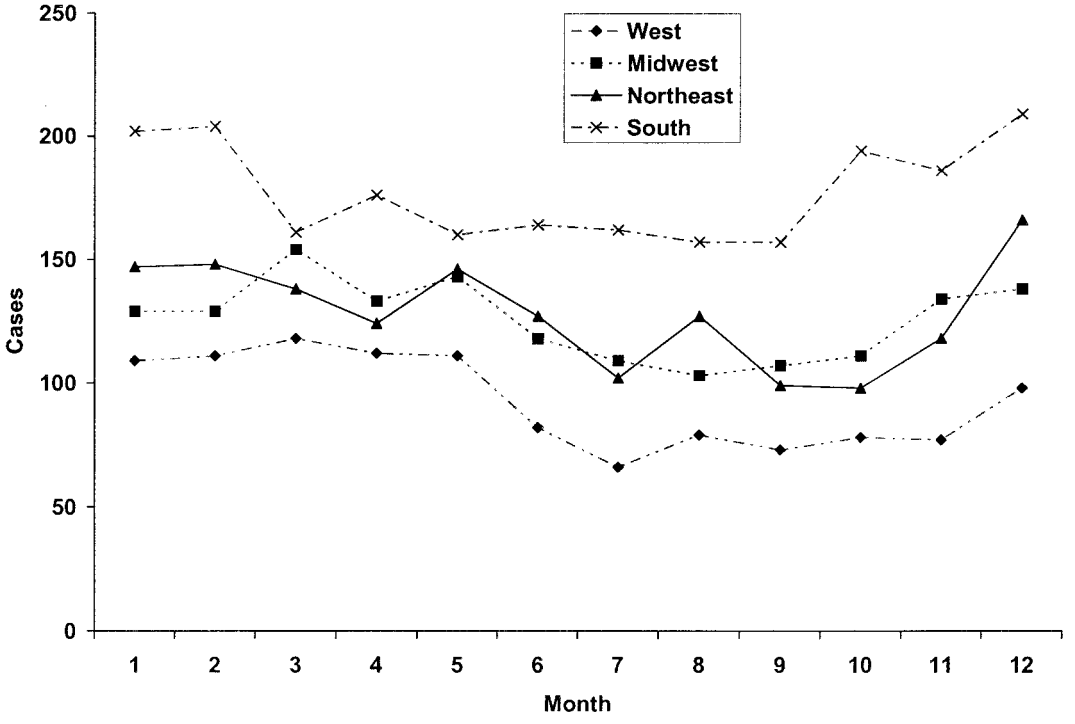

Fig 5. Seasonal variation in the number of KD cases in 4 census regions: West, Midwest, Northeast, and South.

mined because of insufficient clinical information provided in the database.

DISCUSSION

This study provides epidemiologic information on KD in the United States over 10 years, during which the incidence of KD increased. Seasonal variation in the number of KD cases was noted, and the seasonal pattern seems different in the South. Length of hospitalization for KD shortened between 1988 and 1990. This possibly was attributable to the increasing adoption of the combined single intravenous immunoglobulin (IVIG) infusion treatment strategy, which was published in 1991.[16]

The incidence of KD was recently studied and reviewed by Belay et al.[13] Using data collected from 4 West Coast health maintenance organizations, the authors found that the incidence for children <5 years old ranged from 9.0 to 19.1 per 100 000 persons per year. Other studies have reported similar incidences: Connecticut, 18.8, in 1993–1996[9]; San Diego, 9.3 to 15.5, in 1994–1998[12]; and Washington State, 6.5 to 15.2, in 1985–1989.[17] In this study, the incidence per 100 000 children <5 years old was similar to previous studies: from 8.1 in 1988 to 18.5 in 1997 with a trend of increasing incidence over 10 years. The trend of increasing KD incidence has been reported by Taubert who used data from a survey of children's hospitals.[18] Increasing incidence of KD over time was also seen in Japan.[4] The highest incidence of KD reported in the United States was from Hawaii with an incidence 47.7 per 100 000 children <5 years old.[9] Studies from Japan reported a much higher incidence of 108.0.[7]

Increasing recognition of KD diagnosis and awareness of the need for hospitalization and treatment for KD by clinicians may have contributed to the increasing incidence of KD seen in this study. However, it is also possible that more children who do not meet the diagnostic criteria[19] (recently revised by the American Heart Association [AHA]) are diagnosed with KD. In a study from a tertiary children's hospital, Witt et al[20] reported that 36% of the children diagnosed with KD did not meet the AHA criteria. In addition, the proportion of children who did not meet the diagnostic criteria rose from 1991 to 1997. It may be difficult to extrapolate experience from a single institution to a nationwide trend of increasing diagnosis of patients who do not meet AHA criteria. However, if this trend existed in other hospitals or regions, the incidence of KD may continue to rise.

Another possible contributing factor to the increase of KD incidence is the fast growing Asian-American population in the United States. From 1990 to 2000, Asian-American population has increased by 52.4% in the United States.[21] The proportion of US population who are Asian-American has increased from 2.78% in 1990 to 3.64% in 2000.[21] How much of the increase in KD incidence is attributable to increasing Asian-American population and how the continuing increase in Asian-American population is going to affect the incidence of KD in the future requires additional investigation.

The peak age of KD has been reported at 1 to 2 years by previous studies. In Japan, patients <2 years old accounted for 54.1% of all KD cases in 1995–1996.[22] In contrast, patients <2 years old only accounted for 36.6% of cases in this US sample. Patients ≥10 years old accounted for <1% of cases in Japan, but accounted for 4.4% in this study. Other studies from single institution experience in the United States have also reported a high proportion of

children ≥10 years old (5.6%–7.5% of all cases).[23,24] Therefore, the age distribution of cases in the United States seems to be wider compared with cases in Japan. This finding has important clinical implications, because older children with KD are more likely to be diagnosed late, have a higher rate of cardiovascular complications,[23,24] and have a higher mortality rate as reported in the present study. Factors such as differences in demographic (eg, race and ethnic composition) and geographic characteristics (eg, climate, altitude) between the United States and Japan may contribute to such a difference. Future studies are needed to examine this speculation.

Although all studies on KD have shown a male predominance, the male-to-female ratio had ranged widely from 1.16 to 1.85 in different studies.[7,13,14,17] It is likely that the variations in the male-to-female ratio reported by previous studies are attributable to small sample sizes and different geographic areas and time frames from which data were obtained. In the present study, the male-to-female ratio from this national sample was 1.54, which seems to be between the ratios previous reported. This ratio also seems to be slightly larger than the 1.36 reported by a recent survey in Japan.[7]

The seasonal variation of KD has been reported previously. Bell et al[8] reported the 1976–1980 data from Centers for Disease Control and Prevention surveillance and found seasonal variation of cases reported to the Centers for Disease Control and Prevention. This pattern was later reported from the 1991–1993 surveillance by Khan et al.[14] A similar seasonal pattern was also noted from studies in Japan.[22,25] In the present study, seasonal variation was also found, and this pattern remained similar over the 10 years of the study period. Cases from the South region showed a pattern different from other regions: peak incidence in December through February and remained lower from March to September. The decrease of incidence in the South began in March, which was 3 months earlier than other regions. It is speculated that such regional variation in the seasonal pattern may be attributable to differences in the climate of these regions. In support of this, Bronstein et al[12] found the incidence of KD in San Diego correlates with temperature and rainfall. Future studies are needed to investigate the effect of climate on the epidemiology of KD.

The pattern for the day of hospital admission may reflect patients' care-seeking behavior. Parents may take their children to doctors before the weekend comes, which could explain the higher number of admissions on Fridays, and may wait until Monday to see a doctor if their children become ill over the weekend, which could explain the higher number of admissions on Mondays.

Outcomes of children affected by KD are generally good. Mortality attributable to KD is rare. Deaths are usually from cardiovascular complications. Checchia et al[26] reported that 9 patients with KD from the United States who required cardiac transplantation because of coronary and myocardial involvement. The mortality rate in the present series was 0.17%. This rate seems to be slightly higher than 0.08% reported from the Japanese series.[22] The higher mortality rate in the United States could be explained by the higher proportion of children ≥10 years old who had a higher in-hospital mortality rate than children <10 years old.

Limitations

There was a significant amount of missing data in the coding of race and ethnicity of the patients. Therefore, the incidence by race and ethnicity of the study population could not be analyzed. The incidence of coronary aneurysm, a major long-term sequela of KD, cannot be reliably calculated from the NIS database either. Because the NIS database is compiled from multiple states that do not necessarily follow a uniform reporting system, many may not have reported secondary diagnosis. In addition, treatment using IVIG, which has become a standard for preventing coronary aneurysm formation in patients with KD, could not be determined in the NIS data. IVIG treatment was listed as the Principal Procedure in many patients. However, many patients had KD and "diagnostic echocardiography" listed as the Principal Procedure but did not have IVIG listed.

There is also a potential for overestimating KD using an administrative database. Patients who do not meet the AHA criteria and are discharged with a diagnosis of "rule out Kawasaki disease" are likely to be coded as KD. In the NIS database, it is not possible to estimate how many patients who do not meet the AHA criteria are being diagnosed as KD because detailed clinical information is not listed in the database.

CONCLUSION

KD affects mainly children under 5 years of age, with a peak incidence in children 1 to 2 years of age. This study suggests that the incidence of KD is rising over time. An active surveillance system may be needed to determine the cause of increasing KD incidence. Compared with reports from Japan, the age distribution of patients in the United States seems wider. There is a male predominance with male-to-female ratio 1.54 to 1. Although KD occurs year-round, the lowest incidence is seen from July through September. Such seasonal variation did not change over the 10 years of study, although the seasonal pattern varied in different geographic areas. Mortality from KD is rare, although children ≥10 years old are at higher risk.

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