ABSTRACT. Objective. Kawasaki disease (KD) is the most common acquired heart disease in children worldwide. The incidence of KD varies among different countries, with Asian countries supposedly having higher incidences than Western countries. However, the incidence of KD in Taiwan has not been well investigated.

Methods. Since the implementation of Taiwan’s National Health Insurance (NHI) in 1995, NHI has covered health care for >96% of its population. Using the NHI database from 1996 to 2002, we investigated epidemiologic features of KD (International Classification of Diseases, Ninth Revision, code 446.1), the rate of coronary artery aneurysm formation (International Classification of Diseases, Ninth Revision, code 414.11), and the change in incidence during the recent 7 years. We also compared the annual incidences in Taiwan with those reported by other countries.

Results. During the 7-year study period, KD occurred most frequently in the summer and least frequently in winter. It is interesting that the highest peak occurred in the summer of 1998 at the same time that Taiwan’s enterovirus 71 epidemic was occurring. Ninety-one percent of KD cases occurred in children who were <5 years old, and the male-to-female ratio was 1.70:1. Recurrence of KD was found in 1.3% (94 of 7305) of these children, and coronary artery aneurysm was found in 7.3% (536 of 7305). The annual incidence per 100 000 children was 146 in children <1 year old, 98 in 1-year-old children, 51 in 2-year-old children, 28 in 3-year-old children, 19 in 4-year-old children, and 5.3 in 5- to 9-year-old children; the incidence of KD decreased with increased age. The overall incidence was 66 cases per 100 000 children <5 years old from 1996 to 2002 with the annual incidence not differing significantly during the 7-year study period.

Conclusions. KD in Taiwan occurs more frequently in boys and in the summer months. During the 7-year study period, the annual KD incidence in Taiwan of 66/100 000 in children <5 years old was the second highest in the world after Japan. Pediatrics 2004; 114:e678-e682. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0726; Kawasaki disease, age distribution, annual incidence, season.

ABBREVIATIONS. KD, Kawasaki disease; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Kawasaki disease (KD) is an acute systemic febrile illness of unknown cause, predominantly affecting children who are <5 years old. Initially described in 1967 by Tomisaku Kawasaki,1 it is now the most common cause of acquired heart disease in children in the developed world. Although usually self-limiting, KD is associated with a range of complications, the most important being the development of life-threatening coronary artery abnormalities.

Reported incidences of KD in different countries vary widely. For example, Japan has the highest annual incidence in the world. It reported 100 to 110 KD cases per 100 000 children <5 years old between 1995 and 1998 but with ~200 cases per 100 000 in times of epidemic.2–5 Beijing reported annual citywide incidence of 18.2 to 30.6 per 100 000 from 1995 to 1999,6 and Hong Kong reported an annual incidence of 25.4 per 100 000 from 1989 to 1994 and 32 from 1994 to 2000.7,8 Among the annual incidences reported for Western countries, the United States reported 17.6 and 17.1 cases per 100 000 children <5 years old in 1997 and 2000, respectively,9 and from 1996 to 1999, the United Kingdom reported 5.5 per 100 000 children <5 years old in the whole population but 14.6 per 100 000 among Asian children with parents from the Indian subcontinent.10 Australia had annual incidences of 3.7 per 100 000 from 1993 to 1995, and Sweden had 6.2 from 1990 to 1992.11,12 Why the incidence rates vary among countries remains unclear, but the difference possibly is related to a combination of factors, including race/ethnicity, environmental factors, and possible circulating infectious pathogens.

The incidence of KD has not been well investigated in Taiwan. Since the implementation of National Health Insurance (NHI) in Taiwan in 1995, >96% of the total population in Taiwan has received medical health care coverage from this universal national health care system.13 The resulting database contains information on NHI-covered patients who have been given inpatient and outpatient care since the system was implemented. Taiwan’s hospitalization health
care database makes possible the epidemiologic analysis of KD, because almost all patients with KD in Taiwan are hospitalized to receive intravenous immunoglobulin treatment. Using the NHI data, we analyzed the epidemiologic characteristics of KD and investigated the change in incidences during a recent 7-year period.

METHODS

Hospitalization health care records were collected from NHI databases from 1996 to 2002. The NHI databases contained health care data from >95% of all the hospitals in Taiwan and >95% of the population receiving health care. From this database, we selected hospitalized patients who were <18 years old and met criteria listed for KD, on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for KD (446.1) listed as the major or the second diagnosis. We analyzed KD-associated hospitalizations by age group, gender, month of admission, and year. Duration, cost, and regions of hospitalizations were also analyzed. In Taiwan, there are 22.6 million people and the land area is 36188 km², so the population density is 625/km². Most (95.6%) of the population live in the western part of Taiwan, where we divided into northern, central, and southern regions, and only 5.4% live in eastern Taiwan, where medical care and socioeconomic status are underprivileged. There are 23 academic medical centers, 80 regional hospitals, and 435 district hospitals, typing by the hospital size, care, and teaching capacity.

The annual incidences of KD were calculated by dividing the number of KD-associated hospitalizations for children <18 years old by the population of children the same age as reported between 1996 and 2002 by Taiwan census data. The annual incidences of KD were expressed as number of hospitalizations per 100 000 children. Among Taiwan’s NHI database of cases listed as having KD were also included patients who met criteria listed for coronary artery aneurysm, on the basis of the ICD-9-CM code for coronary artery aneurysm (414.11). The incidence of coronary artery aneurysm was calculated by dividing the number of cases with coronary artery aneurysm plus KD by the total number of KD patients.

Statistics

We analyzed the data with SAS statistical software (Version 8.2; SAS Institute, Cary, NC). Data were expressed as mean (standard deviation), median (range), or percentage (number). Annual incidence of KD used the census population as the denominator. The differences among continuous variables was measured by t test. The difference of annual incidences among various age groups, the difference of annual incidences in different years, and the difference in seasonal distribution were measured with goodness-of-fit χ² test. The difference in male-to-female ratio between infants and children who were >1 year old was measured using Pearson χ² test. P < .05 indicated statistical significance.

RESULTS

Overall

There were a total of 7679 hospitalizations for KD among 7305 children who were <18 years old in Taiwan from 1996 to 2002, and 5.1% (374) of the hospitalizations were for transfer to medical centers for re-treatment or recurrence of KD. Their mean age ± standard deviation was 2.17 ± 2.21 years, and the male-to-female ratio was 1.70:1. Recurrence of KD occurred in 1.3% (94) of the children. Children with recurring KD had their first attack at 1.51 ± 1.41 years, which was significantly younger than the mean age of KD cases without recurrence (P < .001). The median (range) of the interval between the first attack of KD and the second attack was 145 (9–1891) days. Eighty-five percent (80 of 94) of the second attack occurred within 2 years after the first episode.

Coronary artery aneurysm was found in 7.3% (536) of the children. Age and gender did not affect the percentage of coronary artery aneurysm.

Seasonal Distribution

Distribution of KD among the seasons is shown in Fig 1. During the 7-year study period, KD occurred most frequently (36.3%) in summer, least frequently (18.5%) in winter, 23.0% of the time in spring, and 22.2% of the time in autumn (P < .001). It is interesting that the highest peak of KD occurred in the...
summer of 1998, at which time there was a large-scale epidemic of enterovirus 71.14,15

Age-Specific Annual Incidence

Age distributions and cumulative percentages of KD are shown in Fig 2. Most (91%) of the KD cases occurred in children who were <5 years old, with 63% occurring in children who were <2 years old. The age distribution in infants, children <1 year old, is shown in Fig 3. Although infants had the highest incidence of KD, this disease occurred much less frequently in infants who were <3 months old than in infants who were >3 months old. The annual incidence per 100 000 infants <3 months old was 40.6, significantly lower than that (180.4 per 100 000) of 3- to 11-month-old infants (P < .01). The age distribution of infants in Fig 3 shows a peak at the age of 7 months.

The age-specific annual incidence according to gender is shown in Fig 4, and the annual incidences of KD in boys were higher than those in girls regardless of age groups. The male to female ratio (1.93) in the infants who were <1 year old was significantly higher than that in children who were ≥1 year old (1.59; P < .001). The annual incidence was 146 per 100 000 in children who were <1 year old, 98 per 100 000 in 1-year-old children, 51 per 100 000 in 2-year-old children, 28 per 100 000 in 3-year-old children, 19 per 100 000 in 4-year-old children, and 5.3 per 100 000 in 5- to 9-year-old children (P < .01). The annual incidence decreased as age increased.

The annual incidence per 100 000 children who were <5 years old did not change significantly during the 7-year study period: 59 in 1996, 52 in 1997, 72 in 1998, 68 in 1999, 69 in 2000, 76 in 2001, and 71 in 2002 (P = .36). The overall incidence was 66 per 100 000 between 1996 and 2002.

Hospital Stay, Charge, and Regional Distribution

Their mean hospital stay was 5.3 ± 3.6 days, and the mean medical cost was 42 068 ± 34 106 New Taiwan dollars (equal to 1237 US dollars). Sixty percent (25 296 New Taiwan dollars) of the medical cost was drug expense, mainly intravenous immunoglobulin. Sixty-seven percent (5148 of 7679) of hospitalizations were in medical centers, 28% (2154 of 7679) were in regional hospitals, and 5% (377 of 7679) were in district hospitals.

Forty-two percent (3232 of 7679) of hospitalizations were in northern Taiwan, where the estimated annual incidence per 100 000 children <5 years old was 68 during the 7-year study period; 27% (2043 of 7679) of hospitalizations were in central Taiwan, where the annual incidence per 100 000 children <5 years old was 65 during the 7-year study period; 28% (2138 of 7679) of hospitalizations were in southern Taiwan, where the annual incidence per 100 000 children <5 years old was 69 during the 7-year study period; and 3.5% (266 of 7679) of hospitalizations were in eastern Taiwan, where the estimated annual incidence per 100 000 children <5 years old was 39 during the 7-year study period. The estimated incidence of children with KD in eastern Taiwan, where medical care is relatively disadvantaged compared with other areas, may be underestimated because KD cases in this area might be hospitalized to regional hospitals or medical centers in northern or southern Taiwan rather than in eastern Taiwan.

DISCUSSION

In Taiwan, KD occurs most frequently in male children who are <5 years old and during the summer. During this 7-year study period, the incidence, 66 per 100 000 in children <5 years old, did not vary significantly.

Similar seasonal summer clustering also has been
reported for Japan, Korea, and Beijing,\textsuperscript{3,6,16} although in the United States, KD has been reported to occur slightly more frequently in the winter.\textsuperscript{9} One cause of this seasonal clustering may be a seasonal viral or bacterial infection, although this would require additional studies.

KD also has been found in geographic clusters and family clusters in Japan, where a high association between KD and infectious disease has also been found.\textsuperscript{2–4,17,18} In addition to temporal and geographic clusters, \textasciitilde 2\% of the siblings would develop KD within 1 week of the illness onset of the first case in the household.\textsuperscript{2} In this study, KD occurred most frequently in summer, the highest peak occurring during the summer of 1998, the time of a large EV71 epidemic in Taiwan.\textsuperscript{14,15} However, no previous studies, as far as we know, have found an association between KD and enteroviruses.

In our study, young children <3 months old months had much lower incidence than children 3 to 11 months of age. The highest incidence was found among 6-month-old to 1-year-old children, who have little maternal antibody and who are generally more susceptible to infections. The increase in incidence in KD among children when they are more susceptible to infectious diseases may also suggest that KD might be caused by an infection. In fact, some scientists have examined the evidence supporting the concept that KD is caused by infectious agents. Various infectious agents, including bacterial, viral, chlamydial, and rickettsial organisms, have been implicated as potential causes, as have certain immunologic agents such as bacterial toxin-mediated superantigens.\textsuperscript{19–35} To date, however, no links have been irrefutably found between any of the above-mentioned individual agents and KD.

Although the incidence of KD is more common among Asians, the incidence of the disease varies considerably among different Asian countries. Taiwan had a KD incidence of 66 per 100 000 among children <5 years old between 1996 and 2002. Around the same period, Taiwan’s incidence of KD among children in this age group was lower than that (100–110 per 100 000) reported for Japan but
higher than the incidences reported for Hong Kong (32 per 100,000) and Beijing (18.2–30.6 per 100,000). All of the incidences of KD in these Asian countries were higher than those reported for Western countries, including the United States (17 per 100,000) and the United Kingdom (5.5 per 100,000). The difference in incidence may be related to genetic and environmental or infectious factors. Although children from Taiwan, Hong Kong, and Beijing belong to the same ethnic group, the incidences of KD in these 3 areas vary, with Taiwan seeming to have a much higher incidence than Hong Kong or Beijing, both of which have similar incidences. These findings also hint that environmental or infectious factors may play an important role in the differences in incidence of KD, although we may not completely exclude the possible role of medical care, socioeconomic factors, and surveillance methods in the differences.

CONCLUSIONS

Taiwanese children have the second highest incidence of KD in the world, after Japanese children. In Taiwan, KD occurs more frequently in younger boys during the summer months.

ACKNOWLEDGMENTS

The Kawasaki Disease Research Group of National Taiwan University College of Medicine and National Taiwan University Hospital includes Ding-Shinn Chen, Bor-Luen Chiang, Mei-Hwan Wu, Ping-Ing Lee, Jon-Ming Chen, Chin-Yun Lee, Luan-Yin Chang, Chun-Yi Lu, Jin-Town Wang, Chuan-Liang Kao, Po-Ren Hseuh, Li-Min Huang, Hong-Nerng Ho, Pei-Jer Chen, Yao-Hsu Yang, and Li-Chieh Wang.

REFERENCES

13. Cheng TM. Taiwan’s new national health insurance program: genesis and experience so far. Health Aff. 2003;22:61–76

KAWASAKI DISEASE IN TAIWAN
Epidemiologic Features of Kawasaki Disease in Taiwan, 1996–2002
Luan-Yin Chang, I-Shou Chang, Chun-Yi Lu, Bor-Luen Chiang, Chin-Yun Lee, Pei-Jer Chen, Jin-Town Wang, Hong-Nerng Ho, Ding-Shinn Chen and Li-Min Huang
Pediatrics 2004;114;e678
DOI: 10.1542/peds.2004-0726

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/114/6/e678

References
This article cites 33 articles, 4 of which you can access for free at:
http://pediatrics.aappublications.org/content/114/6/e678.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub
International Child Health
http://classic.pediatrics.aappublications.org/cgi/collection/international_child_health_sub
Cardiology
http://classic.pediatrics.aappublications.org/cgi/collection/cardiology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
Epidemiologic Features of Kawasaki Disease in Taiwan, 1996–2002
Luan-Yin Chang, I-Shou Chang, Chun-Yi Lu, Bor-Luen Chiang, Chin-Yun Lee, Pei-Jer Chen, Jin-Town Wang, Hong-Ner ng Ho, Ding-Shinn Chen and Li-Min Huang

Pediatrics 2004;114;e678
DOI: 10.1542/peds.2004-0726

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/114/6/e678