The Epidemiology and Clinical Features of Kawasaki Disease in Australia

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KEY WORDS
Kawasaki disease, epidemiology, Australia, outcomes

ABBREVIATIONS
CA—coronary artery
IVIG—intravenous immunoglobulin
KD—Kawasaki disease
PMH—Princess Margaret Hospital
WA—Western Australia

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abstract

OBJECTIVES: The current Australian epidemiology of Kawasaki disease (KD) is poorly defined. Previous enhanced surveillance (1993–1995) estimated an incidence of 3.7/100 000 <5 years.

METHODS: We identified all patients hospitalized in Western Australia (current population ∼2.4 million) 1979 through 2009 with a discharge diagnosis of KD. We reviewed demographic, clinical, laboratory, and echocardiographic data from individual patient files and derived age-specific population estimates. KD diagnosis was made using standard criteria.

RESULTS: There were 353 KD cases, with incomplete KD in 34 (9.6%). Male to female ratio was 1.7:1 and median age was 3.8 years (interquartile range 12–60 months). Fifty (18.1%) patients were Asian. Mean annual incidence increased from 2.82 per 100 000 children aged <5 years (95% confidence interval, 1.95–3.99) in 1980 to 1989, to 7.96 (6.48–9.67) in 1990 to 1999, to 9.34 (7.72–11.20) in 2000 to 2009. The highest incidence was 15.7 in 2005. A total of 293 children (83%) received intravenous immunoglobulin and 331 (95.4%) aspirin. Of 282 children who completed echocardiographic studies, 47 (16.7%) had coronary artery (CA) ectasia/dilatation and 19 (6.8%) had CA aneurysms; male gender was significantly associated with CA abnormalities.

CONCLUSIONS: KD epidemiology in Western Australia mirrors that of other industrialized, predominantly European-Caucasian populations. The rising incidence likely reflects both improved ascertainment and a real increase in disease burden. The current Australian incidence is threefold higher than previously reported and similar to the United Kingdom. The CA outcomes, which include the pre-intravenous immunoglobulin era, are comparable to those reported elsewhere.

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WHAT’S KNOWN ON THIS SUBJECT: The incidence of Kawasaki disease is increasing in many countries. The only reported Australian incidence (3.4/100 000 <5 years) is almost 20 years old and the current Australian epidemiology and outcomes are unknown.

WHAT THIS STUDY ADDS: We analyzed 30 years’ total population hospitalization data from Western Australia. Kawasaki disease incidence increased markedly from 1979 to 2009 and is currently 9.34/100 000 <5 years. The epidemiology and cardiovascular outcomes are similar to other predominantly European-Caucasian populations.
Kawasaki disease (KD) is an acute early childhood vasculitis of unknown etiology and the commonest cause of pediatric acquired heart disease in industrialized countries. Kawasaki disease is described in most populations worldwide with remarkably similar epidemiologic and clinical features. The incidence varies widely, with the highest rates in Japan (239.6 per 100,000 <5 years of age), Korea (113.1 per 100,000 <5 years), and Taiwan (69 per 100,000 <5 years). This incidence is increasing in both industrialized countries such as Japan and the United Kingdom, as well as in rapidly industrializing countries such as India. This may reflect both a genuine increase in disease burden and increased disease recognition.

The first Australian case was reported in 1976. The only published incidence, derived from enhanced national surveillance from 1993 through 1995, was 3.7 per 100,000 children <5 years of age, one of the lowest reported worldwide, but anecdotally an underestimate of the true disease burden. We used the unique total population linked data resources available in Western Australia (WA) to define the clinical and epidemiologic characteristics of KD over a 30-year period. WA is broadly representative of the Australian population and these data provide a robust estimate of overall Australian KD epidemiology.

METHODS

Data Collection

The WA population is largely concentrated in the state capital. In addition to 26 general hospitals (9 metropolitan and 17 rural) with pediatric beds, there is a single tertiary pediatric referral hospital, Princess Margareet Hospital (PMH).

All WA residents discharged from a WA hospital with an International Classification of Diseases coding for KD or mucocutaneous lymph node syndrome (ICD9 446.1 and ICD10 M30.3) were identified by the Data Linkage Unit of the WA Health Department. We cross-referenced these data, removing duplicate admissions, with those from PMH (available from 1989 onward), and data on IVIG recipients, from the WA Blood Bank database (available from 2000 onward).

Individual patient medical files were retrieved and reviewed by using a standardized study-specific data collection form. The patient’s clinical, self-reported ethnicity, self-reported Aboriginality, demographic, laboratory, and echocardiographic data were recorded. Ethnicity and Aboriginality data were cross-referenced with standardized Health Department records, based on place of birth. Follow-up echocardiographic data were retrieved from medical files, the PMH Cardiology Department database, and from private pediatric cardiologists’ records.

The PMH institutional Ethics Committee and the Chief Executive Officers and/or Human Research Ethics Committees of all other hospitals approved the study.

Subjects and Case Definitions

Individual patient’s medical file data were reviewed to confirm the diagnosis of KD using the American Heart Association criteria, modified where necessary to allow for the quality of medical record keeping and the study time-frame, which included a period when KD was an unfamiliar diagnosis.

We defined “definite KD” as fever ≥4 days and ≥4 principal diagnostic features; changes in extremities, polymorphous exanthema, bilateral bulbar conjunctival injection without exudate, changes in the lips and oral cavity, and/or cervical lymphadenopathy ≥1.5 cm diameter. If the medical notes included the descriptors “very prominent” or “significantly enlarged” single cervical lymph node, without precise dimensions, lymphadenopathy was included as a principal diagnostic criterion. Patients whose medical notes documented only “cervical lymphadenopathy” without commenting on size were not considered to fulfill the diagnostic criterion for lymphadenopathy. A diagnosis of “definite KD (echo)” was made if the patient had fever ≥4 days and ≤4 principal KD features, plus abnormal CA findings (defined subsequently) on initial echocardiogram. The diagnosis of “incomplete KD” was made if there was fever ≥5 days and 3 principal features of KD, no echocardiographic abnormalities, and no other etiology identified.

We defined “probable KD” as those who had (1) fever ≥5 days and 2 clinical features of KD, (2) 3 or 4 features but inadequate documentation of fever duration, or (3) 3 or more cardinal features who were given IVIG before day 5 with clear clinical response. Patients were excluded if they fell outside these definitions or clearly had another illness.

Recurrence was defined as reappearance of KD features at least 2 months after the initial presentation; representations before 2 months were considered as a recrudescence. Coronary artery (CA) dilatation was defined by using the Japanese Ministry of Health and Welfare criteria. As height is not routinely recorded during acute pediatric hospitalizations in Australia, body surface area could not be calculated to derive CA z scores, precluding use of the American Heart Association definitions of CA abnormalities. The Japanese Ministry of Health criteria define CA dilatation as any CA branch diameter ≥3 mm in children <5 years old and ≥4 mm in children ≥5 years old, or an internal diameter of any branch >1.5-fold greater than any adjacent segment. Aneurysms were classified as giant if they had a >8 mm internal diameter. Older echocardiographic studies, performed when these criteria were not widely used in Australia and CA dimensions were not recorded consistently, were defined as abnormal if the reviewing cardiologist reported “dilated” or “ectatic” CA.
Data Analysis

Age-specific population estimates were calculated from WA data and calculated separately for the <5-year and 5- to 10-year-old age groups. Denominator data for each age group were obtained from publicly available census data from the Australian Bureau of Statistics. Aboriginal population data were obtained from WA government sources. Confidence intervals were calculated assuming the Poisson distribution. Comparisons of proportions were performed by using the Mann Whitney U test and comparisons of proportions were performed by using Fisher’s exact test. Seasonality was assessed by using the Edwards test, which fits a sinusoidal function across monthly case numbers; the P value tests the null hypothesis of no seasonal variation.

RESULTS

Incidence, Age, Ethnicity, and Seasonal Variation

A total of 465 children who had a discharge diagnosis of KD were identified from January 1, 1979 through June 30, 2009. Forty duplicate admissions and 6 children non-resident in WA were excluded. Twelve patients were excluded as their medical files could not be located and 2 because of inadequate documentation allowing a definitive diagnosis. Twenty-three patients had an obvious non-KD diagnosis. Twenty-nine patients were readmitted within 2 months of the initial episode and the second admission was considered a recrudescence. A total of 353 cases were included in the analysis. The majority of patients (249, 70.5%) were <5 years of age. Eighty-seven (24.6%) were aged 5 to 10 years and 17 (4.8%) were >10 years. The mean annual incidence increased over time from 2.82 per 100,000 children aged <5 years (95% confidence interval, 1.93–3.98) from 1979 to 1989, to 7.96 (6.48–9.67) in 1990 to 1999, to 9.34 (7.72–11.20) in 2000 to 2009. The incidence in children age 5 to 10 years was lower, but also increased from 0.7 per 100,000 in 1980 to 1989, to 2.74 per 100,000 in 1990 to 1999, to 3.25 per 100,000 in 2000 to 2009 (Table 1). There was significant year-to-year variation, with the highest incidence in the <5 years age group of 15.7 in 2005 (Fig 1). There was no evidence of seasonal variation (Edwards test, P = .8).

Epidemiologic and clinical features of the cohort are reported in Table 2. The mean age at presentation was 3.87 years (median 3.2 years, interquartile range 1.5–5.6 years) and 223 cases (63.2%) were male; the male to female ratio was 1.7:1. Of the 276 children whose ethnicity was recorded, 50 (18.1%) had at least 1 parent identified as Asian. There were no patients of Aboriginal or Torres Strait Islander origin, based on self-reported Aboriginality at the time of admission.

Clinical Features

Of the 353 children who had KD, 314 children had a definite diagnosis (297 on clinical criteria, 17 on clinical/echo criteria), 34 had an incomplete diagnosis, and 5 children had a probable diagnosis. Of the 34 children diagnosed with incomplete KD, 23 were diagnosed at PMH, where they accounted for 7.9% of 304 total KD cases. Eleven incomplete cases were diagnosed in low-case-load metropolitan and rural hospitals, where they accounted for 22.4% of 49 total KD cases. Oral mucosal changes and polymorphous skin rash were the commonest diagnostic clinical findings (96.5% and 96.0% of patients, respectively) and cervical lymphadenopathy was the least common finding (62.7%) (Table 2). Irritability was the commonest non-diagnostic clinical feature (89.0%), followed by gastrointestinal (59.9%) and respiratory (37.0%) symptoms. Approximately 25% had peripheral desquamation and arthritis as part of the acute presentation. Bacillus Calmette–Guérin vaccine is not given routinely in Australia.

Table 1. Incidence Rate of Kawasaki Disease in WA Children Aged <10 Years

<table>
<thead>
<tr>
<th>Decade</th>
<th>&lt;5 years</th>
<th>5 to 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence (95% CI) per 100 000 Children</td>
<td>Cases</td>
</tr>
<tr>
<td>1980s</td>
<td>2.82 (1.93–3.98)</td>
<td>32</td>
</tr>
<tr>
<td>1990s</td>
<td>7.96 (6.48–9.67)</td>
<td>101</td>
</tr>
<tr>
<td>2000s</td>
<td>9.34 (7.72–11.20)</td>
<td>116</td>
</tr>
<tr>
<td>Total.</td>
<td>6.51 (5.73–7.37)</td>
<td>249</td>
</tr>
</tbody>
</table>

*Cases and person-years to mid 2009.

**Includes 1 case and population in 1979.
documented) were admitted to an ICU for management of hypotension and cardiovascular compromise requiring inotropes (5 patients), myocarditis and ventricular dysfunction (3), encephalopathy (2), young age (<1 month) (2), pericardial effusion (1), and airway compromise owing to lymphadenopathy (1). There were no early deaths and no patients had a documented myocardial infarction.

Cardiovascular Outcomes

A total of 282 of the 334 children with documented echocardiography had complete echocardiographic data, a minimum of an admission echocardiogram and a study 6 to 8 weeks later. Of these 282 patients, 66 (23.4%) had an abnormal echocardiogram; 47 out of 282 (16.7%) had CA ectasia/dilatation, 14 (5.0%) had CA aneurysms, and 5 (1.8%) had giant CA aneurysms. The incidence of aneurysms and giant aneurysms decreased from 12.2% in 1979 to 1989 to 5.2% in 1999 to 2009, contemporaneous with increased IVIG use. The rate of ectasia/dilatation increased over the study period, possibly reflecting improvements in echocardiographic imaging and reporting, and familiarity with KD. Male gender (odds ratio 2.2; 95% confidence interval 1.5–4.6) was associated with CA involvement in those who had ethnicity data and complete echocardiographic data (Table 3). No other demographic or clinical parameters were significantly associated with CA involvement.

DISCUSSION

This is the definitive study of KD epidemiology in Australia to date. We combined the unique population-based data resources available in WA with other validated sources in an attempt to identify all KD discharge diagnoses. We then reviewed all available individual patient files to maximize diagnostic precision. The overall KD incidence of 9.34/100 000 <5 years of age is therefore likely to be an accurate reflection of the current incidence in the WA population and comparable to similar estimates from the United Kingdom5 and other parts of Europe,13,14 from where much of the non-indigenous WA population originated. The current incidence of KD in WA is higher; the first Australian KD case was reported in 1976,8 whereas robust WA population data linkage was established in 1979.14,15 To maintain diagnostic precision, we excluded children not hospitalized during the acute KD illness, but who were diagnosed on subsequent echocardiographic findings, those who were treated outside WA, and those in whom KD was coded but whose medical files could not be retrieved or did not contain sufficient data to confirm the diagnosis. We also used a more conservative definition of recurrent KD than has been used in some other epidemiologic surveys.15,16

The gender and age distribution in WA was similar to that reported elsewhere, with boys more commonly diagnosed and the majority of cases occurring in children aged <5 years. In contrast to Japan, where the peak incidence is at ~11 months of age and ~85% of cases occur in those aged <5 years,2 the median age was 3.2 years and almost a quarter of cases were older than 5 years. Similar, relatively older age distributions have been noted in European populations.5,14 Children of Asian ethnicity born or resident in low-incidence countries have a higher KD incidence than non-Asian children.5,16 In the current study ethnicity data were available for 75% of cases and the true proportion of Asian patients may have been underestimated; the WA Health Department codes ethnicity by country of birth and therefore Australian-born children of Asian descent would not be identified. We also do not have data on the proportion of children of Asian
descent, although census data in 2001 found that 6.5% of the WA population self-reported Asian ethnicity, including 2.7% of Chinese ethnicity. Thus it appears that Asian children are over-represented in our case series, although we are unable to quantify the relative risk.

The absence of cases in Aboriginal children is striking. Aboriginal children account for ∼6% of the total WA pediatric population, and have a much higher rate of hospitalization with infectious diseases than the non-Aboriginal population. A previous Australian KD epidemiology study reported 2 Aboriginal children of a total of 139 KD patients identified by enhanced surveillance.

The overall rate of CA involvement was relatively high (23.4%), partly reflecting the pre-IVIG era during the first decade of study. Boys were more likely to have CA involvement, a finding reported in other populations.

Our study has a number of strengths, particularly the use of complete hospitalization data from a total, relatively stable, and nationally representative population, and individual standardized review of all available patient files. We acknowledge some unavoidable shortcomings in this retrospective study, particularly incomplete ethnicity and echocardiographic data, but these are likely to have resulted in a relative underestimate of KD incidence and of CA complications. This underestimate may have been compounded by non-admitted and undiagnosed cases. Incomplete data resulted in a handful of cases having the unsatisfactory diagnosis of “probable KD,” but the small numbers (1.4% of cases) means that possible misdiagnosis is unlikely to have significantly affected the overall findings.

**CONCLUSIONS**

The incidence of KD in WA, likely reflective of the Australian national epidemiology, is almost threefold higher than previously reported and continues...
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Dr Saundankar designed the study, coordinated the statewide data collection, interpreted the data, and drafted the initial manuscript; Dr Yim designed the study, assisted with data collection, and drafted the initial manuscript; Dr Itotoh assisted with data collection and reviewed the draft manuscript; Ms Payne assisted with data collection and reviewed the draft manuscript; Dr Ramsay assisted with the study, interpreted data, and reviewed the draft manuscript; Dr Kothari assisted with obtaining approval for data collection and reviewed the draft manuscript; Dr Cheng performed statistical and epidemiological analyses, assisted with interpretation, and contributed to drafting and revision of the manuscript; Dr Burgner conceptualized and designed the study, interpreted the data, and drafted the initial manuscript and subsequent revisions; and all authors approved the final manuscript as submitted.

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