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

(Continued on last page)

**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 (65% 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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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 (259.6 per 100 000 <5 years of age), Korea (113.1 per 100 000 <5 years), and Taiwan (69 per 100 000 age),2 Korea (113.1 per 100 000 <5 years).4 The incidence is increasing in Japan2 and the United Kingdom,5 as well as in rapidly industrializing countries such as India.6 This may reflect both a genuine increase in disease burden and increased disease recognition.7

The first Australian case was reported in 1976.8 The only published incidence, derived from enhanced national surveillance from 1993 through 1995, was 3.7 per 100 000 children <5 years of age,9 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,1 modified where necessary to allow for the quality of medical record keeping and the study timeframe, 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.10

Coronary artery (CA) dilatation was defined by using the Japanese Ministry of Health and Welfare criteria.11 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 Ameican Heart Association definitions of CA abnormalities.1 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.1 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 continuous variables 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 children 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 297 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 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-caseload 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 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 perineal desquamation and arthritis as part of the acute presentation. Bacillus Calmette–Guérin vaccine is not given routinely in Australia.

Treatment and Outcomes
The majority of children (95.4%) were treated with aspirin. Of 16 patients without documented aspirin therapy, 6 had a late diagnosis after acute inflammation had resolved, and 6 had incomplete or probable KD. In a further 4 patients, IVIG was given and is probable that aspirin was also prescribed, but this was not clearly documented in the medical chart.

Overall 83% of children were treated with IVIG, widely used in WA from the mid 1980s; 36.6% received IVIG before 1990, compared with 91.3% of children after 2000. IVIG retreatment was given in 16.5% of patients, predominantly after 2000. Twelve children received steroids, mainly as rescue therapy after non-response to IVIG. Of the 33 patients who did not receive IVIG after 1990, 20 presented after 10 days of fever and many probably had resolved inflammation by presentation, although this was not always clear from the medical charts. At least 13 patients would have been expected to receive IVIG, but whether did not receive this treatment or did not have clear documentation of management in the medical chart.

Fourteen (4.1%) of the 349 children who did not receive IVIG (where the location of care was

<table>
<thead>
<tr>
<th>Decade</th>
<th>&lt;5 years</th>
<th>5 to 10 Years</th>
</tr>
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<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, 3.99)</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.

b 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 Kingdom and other parts of Europe, from where much of the non-indigenous WA population originated. The current incidence of KD is almost three-fold higher than the previously reported incidence, which was derived from enhanced national surveillance almost 20 years ago. Extrapolating these findings to the Australian population suggests there are approximately 170 to 180 KD cases admitted nationally each year. The number of KD cases that are not diagnosed is unknown.

The rising incidence of KD over the study period is likely to represent both increasing awareness and a true increment in disease burden. In WA, as elsewhere, the incidence of KD has continued to increase despite broad familiarity with the disease. It is possible that the actual incidence of KD in WA is higher; the first Australian KD case was reported in 1976, whereas robust WA population data linkage was established in 1979. 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.

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, 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. Children of Asian ethnicity born or resident in low-incidence countries have a higher KD incidence than non-Asian children. 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.17,18 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,12 and have a much higher rate of hospitalization with infectious diseases than the non-Aboriginal population.18 A previous Australian KD epidemiology study reported 2 Aboriginal children of a total of 139 KD patients identified by enhanced surveillance.9

The overall rate of CA involvement was relatively high (23.4%), partly reflecting the pre-IVIG era during the first decade of study.1 Boys were more likely to have CA involvement, a finding reported in other populations.19

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

### TABLE 2 Demographics, Clinical Features, Classification, Treatments, and Echo Findings in WA Patients With KD 1979 to 2009

<table>
<thead>
<tr>
<th></th>
<th>1980 to 1989</th>
<th>1990 to 1999</th>
<th>2000 to 2009</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean, SD)</td>
<td>3.3 +/- 2.7</td>
<td>3.5 +/- 2.5</td>
<td>4.2 +/- 3.4</td>
<td>3.9 +/- 3.0</td>
</tr>
<tr>
<td>Male</td>
<td>26/41 63.4</td>
<td>86/138 62.3</td>
<td>110/173 63.6</td>
<td>223/353 63.2</td>
</tr>
<tr>
<td>Asian</td>
<td>5/23 21.7</td>
<td>18/126 12.7</td>
<td>29/126 23.0</td>
<td>50/276 18.1</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

| Changes in extremities | 36/39 92.3 | 99/134 74.1 | 121/167 72.9 | 257/340 75.6 |
| Polymorphous exanthem  | 41/41 100.0 | 100/138 94.2 | 168/173 97.1 | 339/353 96.0 |
| Bulbar conjunctival injection | 36/39 92.3 | 118/137 86.1 | 151/167 90.4 | 306/344 89.0 |
| Changes in the lips and oral cavity | 36/39 92.3 | 132/136 97.1 | 185/170 97.1 | 334/346 96.5 |
| Cervical lymphadenopathy | 24/37 64.9 | 78/132 59.2 | 106/165 64.2 | 210/335 62.7 |

Associated clinical features

| Irritability | 37/39 94.9 | 117/134 87.3 | 146/164 89.0 | 300/337 89.0 |
| Arthritis    | 7/22 31.8  | 31/117 26.5  | 36/124 29.0  | 74/263 28.1  |
| Perineal desquamation | 9/24 37.5 | 25/104 24.0 | 23/91 25.3 | 57/219 26.0 |
| Gastrointestinal symptoms | 27/38 75.0 | 68/133 51.1 | 95/149 63.8 | 191/319 59.9 |
| Respiratory symptoms | 13/35 37.1 | 43/135 31.9 | 61/145 42.1 | 117/316 37.0 |

Classification

| Definite (echo) | 2 4.9 | 4 2.9 | 11 6.4 | 17 4.8 |
| Definite KD     | 34 82.9 | 117 84.4 | 145 85.9 | 297 84.1 |
| Incomplete      | 4 9.7 | 15 10.8 | 15 8.7 | 34 9.6 |
| Probable KD case | 1 2.4 | 2 1.4 | 2 1.2 | 5 1.4 |

Treatment

| Aspirin | 37 92.5 | 130 95.6 | 163 95.9 | 331 95.4 |
| IVIG    | 15 36.6 | 120 87.0 | 158 91.3 | 203 83.0 |
| IVIG retreatment | 0 0.0 | 13 10.8 | 34 23.4 | 47 16.5 |
| Steroids | 1 2.8 | 0 0.0 | 11 6.9 | 12 3.6 |

Echo findings

| Ectasia/dilatation | 3 7.3 | 15 10.9 | 29 16.8 | 47 13.3 |
| Aneurysm          | 3 7.3 | 3 2.2 | 8 4.6 | 14 4.0 |
| Giant aneurysm    | 2 4.9 | 2 1.4 | 1 0.6 | 5 1.4 |
| Normal echo       | 14 34.1 | 93 67.4 | 109 63.0 | 218 61.2 |
| Normal baseline only | 14 34.1 | 21 15.2 | 17 9.8 | 52 14.7 |

Not done | 5 12.2 | 4 2.9 | 9 5.2 | 19 5.4 |

### TABLE 3 Risk Factors for Abnormal Coronary Artery Findings on Echocardiography

<table>
<thead>
<tr>
<th>Normal Echocardiogram</th>
<th>Abnormal Echocardiogram</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>130/216 60.2</td>
<td>51/68 77.3</td>
</tr>
<tr>
<td>Age (median/IQR)</td>
<td>3.2 (3.3, 4.0)</td>
<td>2.2 (2.6, 4.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>26/175 16.0</td>
<td>15/53 28.3</td>
</tr>
<tr>
<td>IVIG administered</td>
<td>195/216 90.3</td>
<td>57/66 86.4</td>
</tr>
<tr>
<td>IVIG administered &gt;day 10</td>
<td>26/185 14.0</td>
<td>11/57 19.3</td>
</tr>
</tbody>
</table>

Out of 216 patients with complete normal echocardiograms, ethnicity was reported in 175 and timing of IVIG administration in 195.
to increase. The epidemiologic features and outcomes are similar to those in other predominantly European-Caucasian populations.

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(Continued from first page)
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