Kawasaki disease in New Zealand

Paul Heaton,1 Nigel Wilson,2 Ross Nicholson,3 John Doran,1 Alan Parsons1 and Geoff Aiken1

1Taranaki Base Hospital, New Plymouth, 2Starship Hospital, Auckland and 3Middlemore Hospital, Auckland, New Zealand

Aim: To determine the epidemiology, management and outcome of Kawasaki disease (KD) in New Zealand.

Design: Prospective audit using New Zealand Paediatric Surveillance Unit (NZPSU) Reports.

Setting: Single country 2-year epidemiological study.

Patients: All patients diagnosed with KD in New Zealand reported to the NZPSU from January 2001 to December 2002.

Main outcome measures: Incidence of KD; time to diagnosis; use of intravenous immunoglobulin; cardiac features and outcome.

Results: Forty-nine new cases were identified. The annual incidence was 8.0 cases/100 000 children aged less than 5 years. Age at onset was less than 5 years in 86% of cases. Incidence was 4.6/100 000 for children of European origin, 9.6 for Maori, 12.2 for Pacific Islanders and 32.2 for children of East Asian origin. KD was diagnosed at a median of 6 days from onset of illness. 89% had fever and four or more diagnostic features. All patients had at least one echocardiogram: There was one small (2%) coronary artery aneurysm only; 13 (26%) had mild coronary artery dilatation. Thirty-five per cent did not have an echocardiogram performed four or more weeks from illness onset. 45 (92%) cases received intravenous immunoglobulin at median day six. One death due to occlusive coronary artery disease in a 3-month-old boy with atypical symptoms in whom KD was diagnosed at post-mortem.

Conclusions: The incidence of KD in New Zealand is defined with significantly variable risk according to ethnicity. Most patients received appropriate rapid diagnosis and treatment but there was considerable variation in practice in regard to number and timing of echocardiograms. There was a low coronary artery aneurysm rate (2%). Accelerated vaso-occlusive disease was responsible for the single fatality in an atypical case.

Key words: epidemiology; Kawasaki disease; management; New Zealand.
Approximately 6 weeks following the initial notification to the NZPSU the principal investigator would post a questionnaire to each reporting clinician requesting clinical and epidemiological data on each case. The delayed sending of the questionnaire was intended to give sufficient time for each case to have been adequately managed and for ‘non-cases’ to have been excluded. Each case was identifiable only to the reporting clinician. Other national surveillance units have used similar reporting systems in order to identify selected uncommon disorders including KD.9,10

Patients were managed by clinicians in their own units and the investigators provided no specific advice regarding investigation or treatment of individual cases. Echocardiographic studies were undertaken according to the availability and working practices of individual hospitals. Echocardiography analysis was based on the report provided for each examination. Population data were obtained from the most recent national census.11

Results

Notification and Case Inclusion

Report cards were sent to 179 clinicians in 2001 with a 95% return rate, and to 189 clinicians in 2002 with a 95% return rate. Over the 24-month study period there were 58 notifications, of which three were duplicate notifications. In two cases the clinical notes were untraceable and the cases were excluded from analysis. Following review of the data by three investigators and the referring physician the diagnosis was judged not to be KD in four cases, either because there were too few diagnostic criteria or because there was an alternative diagnosis. Thus, there were 49 new cases of KD. Forty-three were considered definite diagnoses fulfilling all the case definitions, four cases were considered to be probable incomplete cases (not all diagnostic criteria present but clinically considered and treated as KD) and two were possible cases (both late presentations but managed as KD).

Gender and age

Of the 49 new cases 31 were male and 18 female (M : F = 1.7 : 1).

Age range was 2 months to 11 years. 13 cases (27%) were aged less than 1 year and 42 (86%) less than 5 years old. The annual incidence was 8.0 cases per 100 000 population aged less than 5 years. For infants aged less than 1 year the annual incidence was 11.8 cases per 100 000.

Table 1  Incidence and ethnicity (cases aged less than 5 years)

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>No. cases</th>
<th>Population at risk11</th>
<th>Annual incidence (95% CI) per 100 000 aged under 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>42</td>
<td>522 078</td>
<td>8.0 (5.8, 10.9)</td>
</tr>
<tr>
<td>NZ European</td>
<td>18</td>
<td>390 354</td>
<td>4.6 (2.7, 7.3)</td>
</tr>
<tr>
<td>Maori</td>
<td>13</td>
<td>135 120</td>
<td>9.6 (5.1, 16.5)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>8</td>
<td>65 350</td>
<td>12.2 (5.3, 24.1)</td>
</tr>
<tr>
<td>East Asian</td>
<td>6</td>
<td>18 501</td>
<td>32.4 (11.9, 70.6)</td>
</tr>
<tr>
<td>Not stated</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Season and Geography

The month of onset of symptoms was Dec–Feb (summer) in 13 cases (26.5%), Mar–May (fall) in 18 (36.7%), Jun–Aug (winter) in 8 (16.3%) and Sep–Nov (spring) in 10 (20.4%). There was no statistically significant seasonal trend.

When documented, the place of residence was North Island in 35 cases (72.9%) and South Island in 13 (27.1%). The incidence of KD approximated to the distribution of the population throughout the country with 73% of cases occurring in the North Island, home to 75.7% of the population, and 23% in the South Island.

Ethnic Trends

Ethnicity was documented for 45 children (92% of all cases) of whom 42 were aged under 5 years. Nineteen cases were identified as NZ European and three were part-NZ European. Nine were Maori and four part-Maori. Eight were Pacific Island people and one was part-Pacific Islander; of these four were Samoan or part-Samoan, three Tongan, one Niuean and one Fijian. There were five children of East Asian origin and one of part-East Asian origin; of these two were Korean, two Chinese, one part-Chinese and one Japanese.

Annual incidence rates for the 42 cases per 10 000 children aged less than 5 years were calculated: this analysis included 37 cases described as belonging to one racial group, two cases each from two racial groups and one case belonging to three racial groups. Overall, the incidence was 8.0 per 100 000 aged under 5 years. Analysis by ethnic group shows incidence rates of 4.6 for NZ European, 9.6 for Maori, 12.2 for Pacific Islanders and 32.4 for children of Chinese, Korean or Japanese origin (Tables 1,2).

Diagnosis and Admission (n = 49 patients)

Kawasaki disease was diagnosed at a mean of 7.4 days, median of 6 days from the onset of fever (range 0–39 days). In 40 cases (82%) the diagnosis was made within the first 7 days of the illness. KD was diagnosed before the eighth day in 12 of 13 (92%) of infants less than 1 year. The diagnosis was made in a mean of 2.2 days of admission to hospital (range 0–12 days). Of the 48 who were admitted 38 (79%) were diagnosed within 3 days of admission.

In 18 of the 49 cases (37%) fever and five diagnostic features were noted and in 25 (51%) fever and four features. Five cases had fever and three other features only. The single case fatality was an ‘atypical’ case with the diagnosis made at post-mortem.
Clinical Features \(n = 49\) patients

See Table 3 for details.

Laboratory Studies (Mean Values Given and Excluding the Three Late-presenting Cases)

The lowest haemoglobin (Hb) level recorded during the course of the illness was 103 g/L (range 70–135). This trough was noted on Day six (range 3–20) from the onset of the illness.

Maximum leukocyte count (WBC) was \(18.8 \times 10^9/L\) (range 5.0–55.2) noted on Day 5.8 (range 3–18) of illness. In 43/46 cases the peak leukocyte count exceeded \(10.0 \times 10^9/L\).

Peak platelet level was \(577 \times 10^9/L\) (range 266–1497), on Day 8.2 (range 2–19).

Erythrocyte Sedimentation Rate (ESR) was measured in 31 cases (63%). The peak level was 78 mm/h (range 10–180) which was noted on Day 6.8 (range 3–19) of illness. In 29 of the 31 cases the peak level exceeded 30 mm/h.

C-reactive protein (CRP) was measured in 34 cases (69%). The peak level was 144 mg/L (range 7–349) noted on day 5.9 (range 2–17) of illness. In 21 of 34 cases the peak level exceeded 100 mg/L.

Serum albumin was measured in 31 cases (63%). Trough albumin level was 32 g/L (range 17–41) noted on day six of illness (range 3–19).

Evidence of Streptococcal Infection

Evidence of streptococcal infection was present in four of 19 cases where testing was performed. In 11 cases serological tests for ASOT and anti-DNase were performed, these were negative in eight and positive in three patients. In the eight cases where throat swabs were taken there was no growth in six, no result documented in one and positive growth of streptococci in one sample.

Other Investigations

Urinalysis was performed on at least one occasion in 39 cases (80%) and was normal in 27. In eight cases there was sterile pyuria, three had proteinuria, two ketonuria and in one microscopic haematuria was present.

Abdominal ultrasound was performed in six cases and was normal in five. One patient had mild obstructive changes of the urinary tract.

No tissue biopsies were taken.

Cardiac Symptoms and Signs

In two cases (4%) abnormal cardiac symptoms or signs were present. One child had pericardial effusion and one, the fatal ‘atypical’ case, had cardiac failure.

Electrocardiogram (ECG) examination was performed in 35 cases (71%) and showed no abnormality in all 35.

Echocardiography

All cases had at least one echocardiogram performed.

Coronary artery ectasia or dilatation was reported in 13 cases (27%). One small aneurysm of 4 mm was detected after 51 days at a first scan. Two cases showed pericardial effusion, neither of which had coronary artery dilatation (CAD). Two had valvular regurgitation, neither had CAD. One study (the fatal ‘atypical’ case) was reported as showing an atrial septal defect with an aneurysmal fossa ovalis, mild mitral regurgitation but no CAD.

Forty-nine scans were performed within the first 28 days after the onset of illness, 31 within 2 weeks of the illness. The proportion of scans with CAD is shown in Figure 1. Only six of the 11 patients with early CA dilatation had ‘late’ follow-up scan, defined as greater than 28 days from onset of illness. Three of these six had improved or had resolution of CAD. Seventeen (35%) of cases did not have any scan after 28 days.

In total, 15 patients (31% of all cases), all aged less than 5 years, had coronary artery abnormalities noted at some point during their illness. 13 had dilatation, one a small LCA aneurysm and the fatal case had luminal occlusion but not dilatation.

Treatment

Forty-five patients (92%) were treated with intravenous gammaglobulin (IVIG), 2 g/kg, and aspirin. Of the four patients who did not receive IVIG three were the late presenters and one was the fatal
received antibiotics. Between 5 and 100 mg/kg/day, as shown in Table 4. Four children were not being given. The initial dosage of aspirin prescribed varied case by case and in the remaining case no reason was specified for aspirin treatment. In untreated cases one was a late presenter, one was the fatal ‘atypical’ case of a 3-month-old boy in whom the diagnosis was made at post-mortem examination. The case has been reported separately.12

### Table 4: Initial dosage of aspirin

<table>
<thead>
<tr>
<th>Mg/kg/day aspirin</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>80</td>
<td>7</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

‘atypical’ case. IVIG was administered at a median of day six, mean of 5.7 days (range 3–12) from the onset of symptoms and in 39 cases (87% of all those receiving IVIG) the treatment was given within the first 7 days of illness. IVIG was given at a mean of 1.8 days (range 1–8) from admission to hospital.

Three patients had a second course of IVIG (2 g/kg) on account of continuing symptoms, this was given 2, 4 and 7 days after the first course. One patient received IVIG 1 g/kg the day following the initial course and then was treated with methylprednisolone (30 mg/kg/day for 3 days).

Forty-six patients (94%) were treated with aspirin. Of the three untreated cases one was a late presenter, one was the fatal ‘atypical’ case and in the remaining case no reason was specified for aspirin not being given. The initial dosage of aspirin prescribed varied between 5 and 100 mg/kg/day, as shown in Table 4. Four children received antibiotics.

### Outcome

The mean duration of admission was 5.1 days (range 1–12 days), median 4 days. 10 patients (22% of all cases) had a length of stay greater than 7 days. Forty children (80% of all cases) were noted to be receiving (mainly low-dose) aspirin at the time of discharge from hospital.

There was a single fatality from accelerated vaso-occlusive disease of a 3-month-old boy in whom the diagnosis was made at post-mortem examination. The case has been reported separately.12

### Discussion

This is the first prospective study of KD undertaken in New Zealand. The high level of returns from monthly NZPSU reporting cards, and the case-ascertainment methodology lead us to believe that all cases occurring within the study period were reported. There remains the possibility that children with incomplete diagnostic features may never have been diagnosed as having KD and therefore may not have been documented.

Kawasaki disease in New Zealand is primarily a disorder affecting pre-school children. The age distribution and male preponderance from this study are similar to reports from Australia, the UK, USA, Japan and Jamaica.9,10,13–15 Cases were reported every month throughout the year with no clearly defined geographical or seasonal trend. There was no evidence of an epidemic pattern such as observed in Japan in the 1980s.16

With approximately 24 new cases per year, the incidence of 8.0 cases per 100 000 population of children aged less than 5 years is greater than the incidence of 5.1 noted by the retrospective study of Gentles et al. in Auckland children during 1979–1988.8 This may reflect the greater awareness of KD among medical practitioners currently, and the prospective methodology of the current study rather than a real increase. The incidence of KD in New Zealand is significantly greater than observed in Australia 1993–1995 when a prospective survey by the Australian Paediatric Surveillance Unit found an incidence of 3.7. Reports from the UK in 2002 indicate an incidence of 8.1 for children with KD under 5 years, more than double the incidence of 3.4 identified in 1990.5,16 Likewise a rising incidence has been observed in Japan, from 73.8 in 1987 to 111.7 in 1998.4 These reports support a real increase in incidence above and beyond increased physician awareness.

In the current study there were clear differences in the incidence of KD between ethnic groups. Caucasian children suffered about half the incidence compared with Maori children. Although the total number of cases were small the incidence for Pacific island children and East Asian children were, respectively, threefold and over sevenfold that seen in the Caucasian population. Studies from the UK and USA have also shown that within a defined geographical area children of Asian and Pacific Island origin suffer higher rates than their Caucasian peers, even when socio-economic factors are taken into account.5,17 These observations suggest that genetically determined factors determine in part the susceptibility to KD of children from differing ethnic populations.

Cardiac complications can be minimized by the timely administration of IVIG, therefore it is essential that the diagnosis is considered as soon as possible following the onset of symptoms.18,19 Diagnosis and treatment were provided rapidly in this study, reflecting a high standard of paediatric care in New Zealand. Meta-analysis of clinical trials has shown that treatment within the first 10 days of the onset of illness will reduce the incidence of cardiac complications, although the study by Zhang et al. suggests that IVIG may be most effective if given within the first 8 days of illness.20–22 In our study 84% of all cases (and 92% of under-one year olds) were diagnosed and treated with IVIG within 10 days of onset of illness. By comparison the 1993–1995 Australian survey found that only 52% of cases were diagnosed and treated within the first 10 days of illness.5
result in this treatment being administered inappropriately to some children who have viral exanthematous illnesses and not KD. The spectrum of physical findings observed in our study group was similar to those seen in the national studies from the UK, Australia, and Jamaica9,10,15 (Table 5).

Abnormalities of haematological profile and inflammatory markers were most prominent towards the end of the first week of illness. Although most cases had significant changes there were a number in whom elevation of white cells, platelets and inflammatory markers were not striking.

In our study there was limited evidence of streptococcal infection, although specific testing was only performed in 39% of cases. Of 19 individuals so tested, a total of four (<20%) had either throat swab or serological evidence of streptococcal infection. We were concerned specifically about streptococcal infection on account of the frequency of streptococcal illness in New Zealand.

Cardiac symptoms, cardiac signs and ECG abnormalities were rarely encountered in the study group. However, there was a relatively high incidence of mild echocardiographic CAD. Many of these cases were detected on early scanning within 28 days of illness onset. Although ‘transient’ CAD is detected in 40% of KD at a median of 10 days, two-thirds show regression before 6 weeks.24 It is of major concern that one-third of cases in the present study did not have an echocardiogram after 4 weeks.

The design of the NZPSU reporting system is such that individual case notes cannot be identified or reviewed by the study group; therefore individual echocardiograms could not be reviewed by any one investigator. It is likely that at different centres there was some variation of interpretation of what constituted CAD or ectasia. It is also possible, although we believe unlikely, that large proximal coronary artery aneurysms greater than 4 mm were missed. The incidence of coronary artery changes is similar to studies from the UK where 24%, Australia 26%, and Jamaica 28% were so affected.9,10,15 In most instances the coronary dilatation affecting our cases was relatively minor and had resolved by the time of the second or third scan.

The timing of echo studies was very variable with the first study being performed at any time from three to 106 days from the onset of illness reflecting local variation in policy. Some centres have not routinely performed an echocardiogram on admission, the investigation is not required to make the diagnosis of KD neither has echocardiography has not been shown to alter outcome in early presenters who responds promptly to the IVIG administration.

Best practice evidence supports that all patients are scanned at diagnosis.25 Some authorities recommend that studies be performed at 10–14 days and 6–8 weeks after the onset of disease in all cases.25–27 Additional echocardiographic studies are appropriate for those with abnormal cardiovascular findings, abnormal ECG, failure of response to IVIG, late presentation >14 days and atypical cases where there is diagnostic uncertainty; also when there is likelihood of developing coronary abnormalities including aneurysms and coronary thrombus. However, there is no evidence that further scanning beyond 6–8 weeks is routinely indicated if studies have shown normal coronary arteries.22–30 During the acute phase of illness we recommend that children with coronary artery aneurysms >4 mm in diameter should have at least weekly studies to monitor for aneurysm progression and thrombus formation. Depending on the size of the aneurysms scanning should be repeated 6–12 monthly.25 In ‘incomplete’ cases of KD, more common in infants aged less than 6 months of age, when there is fever for five days and less than diagnostic features, echocardiography may reveal dilatation, ectasia, perivascular brightness or lack of the normal tapering of the coronary arteries. Such children should receive treatment with IVIG.27

A total of 92% of all cases were treated with a single course of IVIG 2 g/kg, administered as soon as the diagnosis of KD had been considered. Only the remaining 8% who were late presenting cases and the atypical case did not receive IVIG. In the Australian study there was greater variability in the IVIG dosing regime with 78% of those receiving IVIG having 2 g/kg.9 In the British study no patient received 2 g/kg of IVIG administered as a single dose as the survey had been undertaken prior to studies indicating the preferred dosage regime.14,20,31

Our current study noted there was greater variation in the dose of aspirin administered during the acute phase of the illness. The trend was for most patients to be treated with high dose of aspirin (80–100 mg/kg/day) rather than a moderate dose (30–50 mg/kg/day) regimen that may be better tolerated. The Terai and Schulman meta-analysis showed no additional benefit from using high dose (80–100 mg/kg/day) aspirin in reducing the incidence of coronary artery abnormalities.31 For this reason, we recommend using 30 mg/kg/day in the acute phase of illness and then 3–5 mg/kg/day once the fever has settled.25

The fatal case raises a number of issues and illustrates the problem of ‘atypical’ or ‘incomplete’ KD. Such cases will of necessity be less likely to receive rapid diagnosis and treatment. Table 5 indicates...
that such fatal cases worldwide are often diagnosed only at post-mortem, and contribute disproportionately to case fatality rates. Of the nine cases diagnosed post-mortem in Table 5, at least four were ‘atypical’. Six were documented as being White boys (no details for the remaining cases), and at least three had vaso-occlusive disease (pathological detail not documented in any of the remainder). It has been noted that accelerated vaso-occlusive disease poses specifically a particular diagnostic problem as there may be severe coronary artery luminal narrowing despite the unremarkable echocardiographic appearance of coronary artery diameters.\(^7\)\(^8\) We speculate that these fatal cases, which could be considered as falling within the infantile Polyarteritis Nodosus range of the KD spectrum, may follow a significantly different pathophysiological pathway to that of ‘typical’ KD. Such cases warrant further study in order to permit more rapid identification and to develop more effective management.

Acknowledgements

Dr Nigel Dickson and Melissa Carter, NZPSU, provided valuable advice and practical support. The NZPSU is funded by the New Zealand Ministry of Health. Judith Dinsdale, Taranaki Base Hospital, provided clerical and organizational help. Dr Michael Fernando, Taranaki Base Hospital, Dr Nigel Dickson and Melissa Carter, NZPSU, provided valuable assistance with establishment of the database. We thank all the Paediatricians who participated in this study.

References


Appendix

Case Definition (Based on Rowley AH and Schulman ST, Pediatric Clinics of North America, April 1999):

Cases were diagnosed as KD on the basis of the following clinical criteria:
Fever for 5 days or longer and at least four of the following:
1. changes of the peripheral extremities including reddening and oedema of palms and soles, also desquamation of skin.
2. polymorphous exanthema.
3. bilateral conjunctival congestion.
4. changes of the lips and oral cavity.
5. acute non-purulent cervical lymphadenopathy, and disorder not explained by any other disease process.

KD was also diagnosed if patients had coronary artery abnormalities even if other clinical criteria were not satisfied.