Kawasaki disease in Australia, 1993–95

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Abstract

***Aim*—To describe the epidemiology, management, and rate of cardiac sequelae of Kawasaki disease in Australia.**

***Design*—Cases were notified to the Australian Paediatric Surveillance Unit, an active national surveillance scheme, from May 1993 to June 1995.**

***Results*—139 cases of Kawasaki disease were confirmed. In 1994, the annual incidence was 3.7/100 000 children < 5 years old. Sixteen children were not admitted to hospital. Coronary artery abnormalities were reported in 35 (25%) children. Two patients were diagnosed at postmortem examination. Sixty six per cent of patients were diagnosed within 10 days of onset and 81% of these received intravenous gammaglobulin within 10 days. Forty five of the notified children did not fulfil the study criteria because of streptococcal infection or insufficient clinical criteria. One child with streptococcal infection had coronary artery dilatation.**

***Conclusion*—Diagnosis of Kawasaki disease was delayed beyond 10 days in one third of patients, and almost 20% of children who could have received gammaglobulin within 10 days did not. The distinction between Kawasaki disease, streptococcal infection, and other possible diagnoses is problematic in some children.**

(*Arch Dis Child* 1998;**78**:33–39)

Keywords: Kawasaki disease; epidemiology; classification

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Accepted 17 September 1997

In 1967, Kawasaki described 50 children in Japan with a new distinctive clinical entity, "mucocutaneous lymph node syndrome", thought to be a benign childhood illness.[1] In the early 1970s, Melish *et al* reported 12 children from Honolulu with the same illness pattern.[2] Kawasaki disease has now been reported worldwide.

Kawasaki disease is a systemic vasculitis which predominantly affects children under the age of 5 years. Despite recent advances in treatment and research exploring a superantigen mediated role in the aetiology of Kawasaki disease,[3–5] its cause remains unknown and, as such, no diagnostic test is available. Thus diagnosis, clinical management, and research depend on a definition described by a constellation of clinical symptoms and signs. The principal advantage of timely diagnosis of Kawasaki disease is the potential to prevent the complication of coronary artery abnormalities by early treatment with intravenous gammaglobulin (IVGG).[6–9]

In Australia, information about Kawasaki disease was collected in a national study conducted through the Australian Paediatric Surveillance Unit (APSU) from May 1993 to June 1995.[10] The primary study aim was to record the epidemiology, current management, and rate of cardiac sequelae of Kawasaki disease. Analysis and comparison of our results with other reported findings raised questions about the classification of Kawasaki disease and the inclusion and exclusion criteria used for clinical practice and research. Our study includes both inpatient and outpatient cases and reports cases which did not satisfy study criteria. Some of the possible barriers to timely diagnosis and appropriate management are discussed. Preliminary data were reported in 1995,[11 12] and the results of the completed surveillance form the basis of this report.

Methods

CASE ASCERTAINMENT

Cases of Kawasaki disease were collected through notification to the APSU, which operates active national surveillance by sending a monthly reply paid report card to over 900 clinicians (predominantly paediatricians) throughout Australia. Clinicians are asked to tick either the "nothing to report" box or to mark the number of cases of selected rare diseases that they have seen over the preceding month. Between May 1993 and June 1995, Kawasaki disease was one of the conditions listed on the APSU card. Before Kawasaki disease was listed on the card, all clinicians on the APSU mailing list were sent background information and diagnostic criteria on Kawasaki disease and instructions for notification.

At the end of each month, the APSU provided the Kawasaki study group with the names and contact addresses of all clinicians who had reported one or more cases of Kawasaki disease. Clinicians notifying a case of Kawasaki disease to the APSU were sent a reply paid questionnaire which requested demographic, diagnostic, laboratory, and management information about each case. Patient confidentiality was maintained by limiting recording of individual identifiers to the first two letters of each patient's first and last names, their date of birth, and postal code.

DEFINITION AND INCLUSIONS AND EXCLUSIONS

Cases were included in the study if the patients were less than 16 years of age, had fever for five or more days, and had any four of these five clinical criteria: (1) bilateral conjunctival injection; (2) oral mucosal changes, such as injected

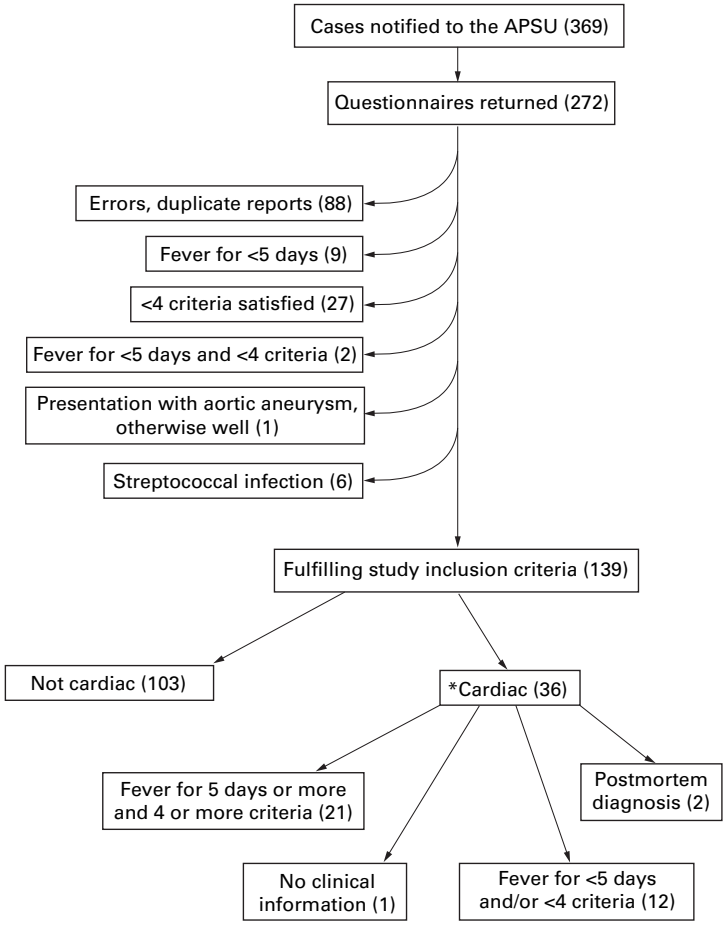
pharynx, dry cracked lips, or strawberry tongue; (3) changes of the peripheries, such as hand or foot oedema, erythema, or desquamation (which may be in the napkin area and occur some time after presentation); (4) rash; or (5) cervical lymphadenopathy greater than 1.5 cm in diameter. Patients were also included if aneurysm, dilatation, or ectasia of the coronary arteries were seen at echocardiography, even if the other clinical criteria were not satisfied. The definition specified that patients with either documented measles or streptococcal infection should be excluded.

Notified cases were excluded if they were duplicate reports or known errors of reporting (that is, diagnosis outside the study time, incorrect diagnoses, the wrong box ticked on the reporting card, or insufficient information supplied). All other patients notified are included in this report, and are identified as either patients fulfilling study inclusion criteria, patients excluded because of documented streptococcal infection, or patients excluded with insufficient clinical criteria.

ANALYSIS

Patients were categorised by clinical signs (duration of fever and number of clinical criteria), echocardiographic features, documented infection, and admission to hospital. All echocardiograms reported were completed during the acute illness. Reports of echocardiographic abnormalities were not validated. A patient was considered to have group A streptococcal infection if there was a positive throat swab culture or an antistreptolysin O titre greater than 400 IU/l or an anti-DNase B titre greater than 160 kIU/l. Incidence was calculated for 1994, the year when data were collected for the entire calendar year, and when the APSU report cards and questionnaire response rates were of acceptable quality.

Findings are reported separately for patients satisfying study inclusion criteria and those who did not. Data were stored using a clinical reporting system and analysis performed with SPSS/PC for windows and Epi Info 6.[13] Continuous variables were compared using the Mann-Whitney U test and proportions compared using exact binomial 95% confidence intervals (95% CI).



*reported coronary or other arterial abnormalities

Figure 1 Categorisation of patients notified to the APSU, May 1993 to June 1995.

Results

During the period of this study, there was a monthly card return rate to the APSU of between 80–93%, with an overall return rate for 1994 of 89%. In total, 369 cases were notified. Of these, 272 questionnaires were completed and returned (74% response rate). The response rate was best in 1994 (80%). Sixty five notifications were duplicates and a further 23 were reporting errors, resulting in 184 patients thought by clinicians to have Kawasaki disease. All of these patients underwent echocardiography. Forty five of the 184 patients did not satisfy the study inclusion criteria because they had fever for less than five days and/or less than four of the five clinical criteria, or they had documented streptococcal infection (fig 1). One patient, excluded because of insufficient clinical criteria, was notified when an aortic aneurysm was found in a child whose sibling was known to have had Kawasaki disease. There were 139 patients who satisfied study inclusion criteria.

PATIENTS SATISFYING STUDY CRITERIA

Incidence and demographic features

The estimated incidence from confirmed cases of Kawasaki disease in Australia in 1994 was 3.7/100 000 (95% CI 3.6 to 3.8/100 000) children under 5 years old and 0.59/100 000 (95% CI 0.56 to 0.62/100 000) for children aged between 5 and 15 years old. Sixteen patients (12%) were not admitted to hospital. The boy to girl ratio was 1.8:1 for all patients and 3:1 for those not admitted. The age at diagnosis was available for 135 patients and the median was 2.8 years, with ages ranging from 5 weeks to 14.6 years. Seventy five per cent of patients were aged under 5 years, with 20% under 1 year old at the time of diagnosis (fig 2). When the ages at diagnosis of children admitted and not admitted were compared, children not admitted to hospital were older, though not significantly (median age 3.5 years, 56% under the age of 5).

Most patients with Kawasaki disease were European (72%), with a substantial minority reported to be Asian (14%), and two reported

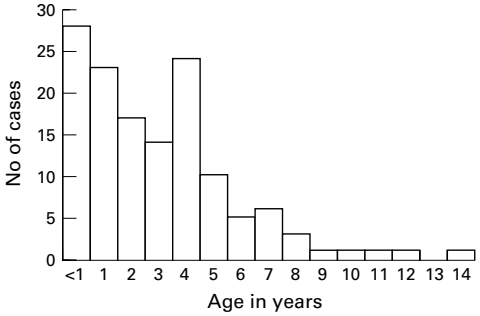


Figure 2 Distribution of age at diagnosis

to be aboriginal. No state was significantly overrepresented in the number of Kawasaki disease notifications for the resident population under the age of 15 years.[14]

Clinical manifestations

The duration to diagnosis from the onset of the first symptom was known for 134 cases, and the median time was eight days. Sixty six per cent of these cases were diagnosed within the first 10 days, with the longest time to diagnosis being 60 days. The median time to diagnosis of cases not admitted to hospital was significantly longer (19 days) than for cases who were admitted (seven days). Time to diagnosis also differed for cardiac (median 9.5) and non-cardiac groups (median 7.0), though not significantly. Cases diagnosed after 10 days of symptom onset were significantly ($p = 0.0008$) older (median 4.3, range 0.2–12 years) than cases diagnosed within 10 days (median 2.0, range 0.1–14.6 years). Although not significant, a higher proportion of cardiac cases who satisfied other clinical criteria were diagnosed at or before 10 days of onset (67%) compared with those included solely on the basis of abnormal echocardiography (42%).

Cervical lymph node enlargement was the least frequently reported cardinal clinical sign (table 1). The oral changes most commonly reported were red lips or strawberry tongue. Other oral changes reported included dry cracked lips, buccal inflammation, pharyngeal injection, and mouth ulcers. Extremity changes were reported to involve the hands and feet and the napkin area, and included desquamation, oedema, and redness. Rashes reported were mainly maculopapular/morbilliform (28%) or macular (25%), but a substantial minority were described as urticarial, pruritic, and scarlatiniform. Many rashes were florid and confluent, others were pale, discrete, and transient. Other non-cardinal symptoms were also reported; respiratory symptoms, mainly cough, were reported for 55 (40%) patients; diarrhoea (24%), vomiting (4%), diarrhoea and vomiting (8%), arthralgia or arthritis (12%).

Investigation findings

The maximum erythrocyte sedimentation rate (ESR), platelet count, and white cell count (WCC) were available for 106, 118, and 108 cases, respectively. The median maximum ESR was 85 mm/hour with an ESR greater than 50 in 75 (71%) patients. The median maximum platelet count was 577×10^9/l, with 88 (75%) patients having a count greater than 450×10^9/l. One patient was thrombocytopenic with a maximum platelet count, while unwell, of 112×10^9/l. The median maximum WCC was 16.5×10^9/l, with 63 (58%) cases having a WCC greater than 15×10^9/l. Abnormal liver function tests were reported in nine patients, with clinical jaundice reported in two of these patients. Although abdominal ultrasound was not done in all patients, hydrops of the gall bladder was reported in 23 children (17%; 95% CI 11 to 24). One child underwent percutaneous drainage of the gall bladder.

Acute management

Treatment used was a varying combination of IVGG, high dose aspirin, and low dose aspirin. In total, 110 (79%) patients received IVGG, 73 (53%) received high dose aspirin, and 102 (75%) received low dose aspirin. All patients given IVGG were admitted to hospital. Ninety one per cent of admitted patients received IVGG. Twenty four children (17%) also received antibiotics during the course of their illness. Of the children who received IVGG, most (86) were given a single 2 g/kg dose. In the remainder, varying regimens were used, including a single dose of 0.4 g/kg (two), multiple treatment doses of 0.4 g/kg (five), one dose of 1g/kg (five) and two doses of either 1g/kg or 2g/kg (12). Five patients were given high dose aspirin and no IVGG. Sixty seven children (48%) received IVGG within 10 days of onset and high dose aspirin. Thirty two per cent of the group treated with IVGG were also treated with low dose aspirin.

Of the 89 children who had the diagnosis made in less than 10 days, 72 (81%) had received IVGG within 10 days. None of the 16 cases not admitted received IVGG. Of the cases receiving IVGG within 10 days of diagnosis, 14 (19%) were reported to have echocardiographic coronary artery abnormalities with five (7%) having coronary artery aneurysms. Of the 34 patients with echocardiographic coronary artery abnormalities, 19 had been diagnosed within 10 days and 14 of these received IVGG in less than 10 days. Although this was a lower proportion than the non-cardiac group the difference was not significant.

Cardiac sequelae

Coronary or other arterial abnormalities were reported in 36 patients. Thirteen children were included because of echocardiographic abnormalities, but did not fulfil the other clinical criteria because they had fever for less than five days (one), less than four clinical criteria (10), both (one), or insufficient information available (one). The child who did not have fever

Table 1 Number and proportion of patients with cardinal symptoms

Symptoms	*No (%)*
Rash	130 (95)
Extremity changes	127 (93)
Oral changes	128 (93)
Eye changes	123 (90)
Lymph nodes > 1.5 cm	59 (43)
Total number of patients	137

and had insufficient clinical criteria had only two clinical signs reported. Three further children had only two criteria reported; none of these had lymph nodes greater than 1.5 cm or eye changes. Seven patients satisfied three clinical criteria with the absence of: lymph nodes greater than 1.5 cm (five), extremity changes (three), oral changes (two), rash (two), and eye changes (one). Two of the 36 children died and the diagnosis of Kawasaki disease was made at necropsy. One child aged 2.5 years arrested six hours after presentation to hospital and the postmortem examination showed intimal fibrous thickening extending from the aorta into the right coronary artery. The second child, aged 8 months, died after rupture of the ascending aorta, and inflammation of the aortic wall was found at postmortem examination, but there were no coronary artery abnormalities detected.

Of the 34 patients with echocardiographic abnormalities, 14 had aneurysms reported (one giant aneurysm), 16 had coronary dilatation, one had coronary ectasia, and three had ectasia and dilatation. Other echocardiographic abnormalities were reported in an additional 10 children who satisfied other diagnostic criteria; pericardial effusion (four), borderline coronary artery abnormalities such as "prominent", "echogenic", or "possible abnormalities" of the coronary arteries (six).

The proportion of all cases which fulfilled study inclusion criteria with documented coronary artery abnormalities was 25% (95% CI 18 to 33). Fourteen (10%, 95% CI 6 to 16) had coronary artery aneurysms. The risk of coronary artery abnormalities for cases satisfying the clinical classification criteria of Kawasaki disease was 17% (95% CI 11 to 25) for coronary artery ectasia, dilatation, and aneurysm and 7% (95% CI 3 to 13) for aneurysm alone.

Excluding patients where the diagnosis was made at postmortem examination, three (19%; 95% CI 4 to 46) of the 16 patients not hospitalised developed coronary artery sequelae, compared with 31 of 121 admitted patients (26%; 95% CI 18 to 34). When analysis was stratified for age, the proportion of children with coronary artery sequelae was similar for the under 5 age group whether children were admitted, 25% (95% CI 17 to 35) or not, 30% (95% CI 7 to 65).

There was a trend for the patients with cardiac complications to be younger than non-cardiac patients and to be boys, but these differences were not significant.

PATIENTS NOT SATISFYING STUDY INCLUSION CRITERIA

Patients with streptococcal infection

Six cases satisfying the clinical diagnostic criteria were excluded because group A streptococcal infection was documented, five with increased antistreptolysin O titre. Their ages ranged from 1.8 to 6.2 years at diagnosis, with three cases under the age of 5 years. One of these had coronary artery dilatation (antistreptolysin O titre > 2000). Two had hydrops of the gallbladder reported. Four received IVGG, and three of these were treated within 10 days of symptom onset. Diagnosis was not made until after 10 days from symptom onset in the two patients who did not receive IVGG. These two patients were not admitted to hospital. The boy to girl ratio was 5:1. The four admitted patients had a maximum ESR of greater than 50 mm/hour. For five children, the maximum platelet count was available and in three it was over 450×10^9/l. The WCC was also available for five patients and was greater than 15×10^9/l in two.

Patients with insufficient clinical criteria

Age at diagnosis was available for 37 of the 39 children with insufficient clinical criteria for inclusion, and ranged from 10 weeks to 14.3 years, with 73% aged less than 5 years. The boy to girl ratio was 1.7:1. Maximum ESR, platelet count, and WCC were available for 23, 31, and 28 children, respectively. The maximum ESR was greater than 50 for 19 (83%) patients. The maximum platelet count was greater than 450×10^9/l for 27 (87%) patients, and the maximum WCC was greater than 15×10^9/l for 14 (50%) patients.

Of the 27 children excluded because they had less than four of the five clinical criteria, 20 had three criteria. Nineteen of these children did not have lymph nodes known to be greater than 1.5 cm. Of these 20 children, the other absent clinical signs were eye changes (12), oral changes (four), and extremity changes (two).

Four patients who did not satisfy the clinical criteria were also documented to have streptococcal infection. Eight patients who did not satisfy clinical criteria were reported to have cardiac abnormalities other than those sufficient for study inclusion: pericardial effusion (three), an aortic aneurysm (one), myocarditis with effusion (one), "query coronary artery dilatation" (one), and "prominent coronary artery" (two).

Twenty two patients were diagnosed within 10 days of symptom onset. In total 24 patients received IVGG, with 16 of those diagnosed within 10 days being treated on or before the 10th day. Five patients received IVGG less than five days from symptom onset.

Discussion

The estimated annual incidence from this study (3.7/100 000/year) is the best available for Australia to date and is similar to figures reported in the British Isles (3.6/100 000/year)[15] and Adelaide (3.9/100 000/year),[16] and less than reported from the US (9.2/100 000/year)[17] for children aged less than 5 years. As expected, the incidence in Australia is strikingly less than reports from Japan (90/100 000/year).[18 19]

The male predominance and age distribution are similar to reports from the British Isles, Japan, and the USA.[15 18–20] The proportion of Australians born in Asia reported in the 1991 census data was 4%,[21] but unfortunately no data are available in Australia that allow direct comparison with the proportion of children from Asian families reported to this study. Two patients reported to this study were aboriginal,

documenting for the first time that this condition occurs in this racial group. The proportion of children reported in Australia to have hydrops of the gall bladder (17%; 95% CI 11 to 24) is over three times higher than previously reported figures.[22 23] This high reported proportion of children with hydrops may be due to more frequent investigation for this abnormality in Australia, or to the use of subjective criteria for diagnosis. Until abdominal ultrasound is performed on all cases, however, and a firm definition of hydrops developed, the true proportion of affected children will not be known.

Results from laboratory investigations (WCC, ESR, platelet count) indicate that a large proportion of children did not have abnormal results at the time of testing. Clinicians would be provided with more meaningful information about the likelihood of results being positive at the time of diagnosis if future researchers also collected information about timing of these investigations in relation to the onset of illness.

Despite current recommendations that all children with Kawasaki disease should receive IVGG within 10 days of onset of fever,[8 9 23–28] we are concerned that nearly 20% of patients in Australia diagnosed within 10 days did not receive this treatment. The different modes and combinations of treatment used also raises concern about clinician awareness of current treatment recommendations, similar to that expressed in the British Isles.[15]

A notable difference between this and other studies was ascertainment of patients not admitted to hospital.[15 16 19 29] In this study, 16 patients not admitted to hospital satisfied the clinical inclusion criteria for Kawasaki disease. Despite a delay in diagnosis and failure to give IVGG to any of these patients, the proportion with cardiac sequelae in this group was similar to that in hospitalised patients. These findings may reflect a difference among echocardiographic findings depending on their timing in relation to clinical course, or they may be identifying a difference between patients admitted and those not admitted. Unfortunately, insufficient information is available to draw firm conclusions. This information is, however, a reminder that studies which sample only hospital cases of the disease could be providing biased information about the severity and sequelae of Kawasaki disease. Although this should not change current recommendations for management, further exploration is warranted to ensure that current outcome predictions are appropriate for this group.

Although the definition used for this study is similar to that used by other research groups, there are some important differences which have implications for incidence figures reported and comparison of findings with previous reports. Of equal importance are the differences among the diagnostic classification systems and inclusions and exclusions used for other studies. For example, data reported for the British Isles included patients with only three or four of their six necessary criteria, provided the clinician was convinced of the diagnosis and no other reasonable explanation could be found.[15] In our study, and in a report from the USA,[20] fever for five days was a necessary criterion, while reports from the British Isles and Japan include fever as one of the six possible criteria, with 10% of cases in the British Isles not satisfying this criterion.[15 19] Our lower reported occurrence of lymphadenopathy may indicate a real difference compared with other studies,[15 20] but could also indicate either that not all adenopathy in Kawasaki disease is greater than 1.5 cm in diameter or that clinicians underestimate the size of adenopathy.

Inclusion of patients with echocardiographic abnormalities, even if they did not satisfy other clinical criteria, may be providing an overestimation of reported cardiac complications for Kawasaki disease. Of the cases satisfying inclusion criteria, 26% had reported echocardiographic coronary abnormalities, a figure similar to that reported in the British Isles (24%) which used similar inclusion criteria.[15] If the 13 patients who did not also satisfy other inclusion criteria were excluded, the proportion of cases with coronary artery abnormalities more closely approximates the rate reported from Japan (13%), a study which only included cases with cardiac sequelae who had four of the necessary six clinical criteria.[19]

There are, however, good reasons for including patients with echocardiographic abnormalities who do not fulfil other criteria. Firstly, if these patients are not included the sensitivity of the classification system will be low.[15] Secondly, patients with cardiac abnormalities only form an important subgroup. Fewer cases with echocardiographic abnormalities, without other sufficient clinical criteria, were diagnosed under 10 days of age compared with those with sufficient criteria. Whether the absence of signs and symptoms is causing the delay in diagnosis is not certain, but further investigation is warranted to determine ways that diagnosis can be made in time to initiate preventive measures. The key may lie in distilling clinical features which prompt clinicians managing these children to arrange echocardiography despite an absence of sufficient criteria for the diagnosis of Kawasaki disease.

The reliability of echocardiographic findings and the type of lesions included are also important when calculating risk of cardiac sequelae. Reports of cardiac sequelae in this study suggest that this is not always straightforward, and deficiencies in the information gathered by this study have limited the interpretation of reported findings. For example, we did not assess the reported echocardiograms and recognise that "overreporting" and "underreporting" of abnormalities by non-expert sonographers may have occurred; nor did we determine the significance of aneurysm *v* slight dilation *v* perivascular brightness. To ensure comparability of study findings, researchers need to make clear their inclusion and exclusion criteria for cardiac abnormalities, use age related criteria for coronary artery size, and where possible provide information about any other aspects of their study which

could affect reported results, such as the timing of echocardiography, whether follow up studies were performed, and whether attempts were made to standardise reporting or assess the reliability of reported findings.

Although information about patients not satisfying study inclusion criteria has been reported, these patients have not been compared with those who satisfied inclusion criteria because their notification was not sought, thus making it unlikely that they are representative of this group. For example, notification could be biased toward cardiac sequelae (in the streptococcal group) or other clinical and demographic features (such as being male and having a high platelet count). They do, however, provide interesting information about some of the problems faced in clinical practice, such as making a decision about treatment of a child with less than four of the clinical signs necessary for a diagnosis of classical Kawasaki disease.

Other studies have reported the clinical features and cardiac sequelae of Kawasaki disease in association with streptococcal infection.[15 16 30–33] Currently, the role of a superantigen in the pathogenesis of Kawasaki disease is being investigated.[3–5] Moreover, it is hard to exclude streptococcal infection when convalescent antistreptolysin O titre or anti-DNase B titres are not routinely collected. Conversely, a positive throat culture for group A streptococcus may indicate throat carriage rather than causal infection. While the relevance of streptococcal and other infections in the pathogenesis of Kawasaki disease remains uncertain, it would seem wise to advise that a bacterial infective cause be looked for in all cases but that treatment with IVGG is given dependent on acute clinical features and a clinical diagnosis of Kawasaki disease.[34] Investigators should also report the number of cases undergoing investigations sufficient to determine the presence or absence of streptococcal infection, so that the true proportion of "cases" which have streptococcal infection, and the proportion of infected patients developing coronary artery abnormalities can be determined.

It has been suggested that a high index of clinical suspicion of Kawasaki disease could improve diagnosis and implementation of preventive treatment. The treatment of cases which did not satisfy study inclusion criteria suggests that clinicians are making decisions about diagnosis and management mindful that these patients could go on to develop the necessary signs and/or cardiac sequelae. In addition, in several patients, IVGG was given early in the clinical course and it is possible that early initiation of treatment has modified the appearance of the clinical manifestations necessary for current classification systems. It is likely that the patients reported here who are being investigated and treated by clinicians but do not satisfy current classification systems, indicate a larger clinical pool of patients with Kawasaki disease. However, further information about the expected outcome, impact of treatment on clinical signs, and the effect of interventions in this group is needed to confirm this suspicion.

Key messages

- A substantial proportion of children with Kawasaki disease does not receive intravenous gammaglobulin within 10 days of symptom onset
- Treatment should be given on clinical grounds regardless of the results of streptococcal throat cultures and serology
- More research is needed to clarify the significance of the type, timing, and prognosis of the echocardiographic coronary artery abnormalities seen in Kawasaki disease
- Until diagnostic tests are available for Kawasaki disease, the challenge is to encourage early diagnosis and management without promoting inappropiate use of treatments

The clinical manifestations reported indicate that a diverse range of types and sites of each of the clinical criteria occur. The clinical features and laboratory results are not pathognomonic. Variation in the sequence of appearance of clinical criteria exists, some features are not expected until after 10 days of illness and some may be transient. These factors contribute to diagnostic difficulties facing clinicians seeing children with possible Kawasaki disease.

To provide good quality care for children with Kawasaki disease, with the aim of reducing the likelihood of coronary artery sequelae, clinicians need to identify cases early and provide timely intervention. There is no doubt that the information currently available suggests that clinicians should be encouraged to have a high index of clinical suspicion about this disorder and implement treatment with IVGG as soon as the diagnosis is made, using established criteria. It is also important that clinicians do not delay treatment while awaiting echocardiography if the diagnosis has been established on clinical grounds. The echocardiogram is not a diagnostic test for Kawasaki disease. At the same time, researchers should take up the challenge to encourage early diagnosis and management without promoting inappropriate use of treatments. This requires that review of the current classification system for Kawasaki disease be undertaken to determine if modifications could be made which may promote earlier diagnosis. At the same time, further information should be collected about patients with proved infections, patients not admitted to hospital, and patients not currently fulfilling classification criteria, but which prompt investigation and treatment.

Many thanks to all the contributors to the APSU and especially the paediatricians who notified patients, the APSU for their assistance, and the Clive and Vera Ramaciotti Foundation and the Financial Markets Foundation for Children who were the principal sponsors of the APSU during the time of this study. Thanks also to Susan Hall and the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health (formerly the British Paediatric Association Surveillance Unit) Kawasaki study group for their advice during the establishment of this study.

1 Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children (Japanese). *Japanese Journal of Allergy* 1967;**16**:178–22.
2 Melish ME, Hicks RV, Larsen E. Mucocutaneous lymph node syndrome in the United States. *Am J Dis Child* 1976; **130**:599–607.
3 Leung DYM, Meissner HC, Fulton DR, *et al*. Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome. *Lancet* 1993;**342**:1385–8.
4 Leung DYM, Giorno RC, Kazem LV, *et al*. Evidence for superantigen involvement in cardiovascular injury due to Kawasaki syndrome. *J Immunol* 1995;**155**:5018–21.
5 Curtis N, Zheng R, Lamb JR, *et al*. Evidence for a superantigen mediated process in Kawasaki disease. *Arch Dis Child* 1995;**72**:308–11.
6 Furosho K, Karriny T, Nakana H, *et al*. High dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984;**ii**:1055–8.
7 Nagashima M, Matsushima M, Matsuoka H. High dose gammaglobulin therapy for Kawasaki disease. *J Pediatr* 1987;**110**:710–2.
8 Newburger JW, Takahashi M, Burns JC, *et al*. The treatment of Kawasaki syndrome with intravenous gammaglobulin. *New Engl J Med* 1986;**315**:341–7.
9 Newburger JW, Takahashi M, Beiser AS, *et al*. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome *N Engl J Med* 1991;**324**:1633–9.
10 Elliott EJ, Chant KG. Rare disease surveillance. *J Paediatr Child Health* 1994;**30**:463–5.
11 Royle J, Isaacs D, Nolan T, *et al*. Kawasaki disease in Australia. *J Paediatr Child Health* 1995;**31**:P22.
12 Sholler G, Royle J, Isaacs D, *et al*. Kawasaki disease in Australia. In: Kato H, ed. *Proceedings of the 5th International Kawasaki disease symposium*. Japan: Elsevier Science, 1995; 69–73.
13 Dean AG, Dean JA, Coulombier D, *et al*. *Epi Info, Version 6: A word processing database and statistics program for epidemiology on microcomputers.* Atlanta: Centers for Disease Control and Prevention, 1994.
14 Australian demographic statistics, ABS Catalogue No 3101.0. *Estimated resident population by age groups.* Canberra: Government Publishing Service, 30 June 1994: 8.
15 Dhillon R, Newton L, Rudd PT, *et al*. Management of Kawasaki disease in the British Isles. *Arch Dis Child* 1993; **69**:631–8.
16 Smith PK, Goldwater PN. Kawasaki disease in Adelaide. A review. *J Paediatr Child Health* 1993;**29**:126–31.
17 Taubert KA, Rowley AH, Shulman ST. Seven-year national survey of Kawasaki disease and acute rheumatic fever. *Pediatr Infect Dis J* 1994;**13**:704–8.
18 Yanagawa H, Kawasaki T, Shigemetsu I. Nationwide survey on Kawasaki disease in Japan. *Pediatrics* 1987;**90**:58–62.
19 Yanagawa H, Yashiro M, Nakamura Y, *et al*. Epidemiologic pictures of Kawasaki disease in Japan: from the nationwide incidence survey in 1991 and 1992. *Pediatrics* 1995;**95**: 475–9.
20 Morens DM, Anderson LJ, Hurwitz ES. National surveillance of Kawasaki disease. *Pediatrics* 1980;**65**:21–5.
21 Basic Community Profile, ABS Catalogue No 2722.0. Census of Population and Housing. Canberra: Government Publishing Service, 1991:4.
22 Choi YS, Sharma B. Gallbladder hydrops in mucocutaneous lymph node syndrome. *South Med J* 1989;**82**: 397–8.
23 Rowley AH, Gonzalez-Crussi E, Shulman ST. Kawasaki disease. *Rev Infect Dis* 1988;**10**:1–15.
24 Rowley AH, Shulman ST. Current therapy for acute Kawasaki syndrome. *J Pediatr* 1991;**118**:987–91.
25 American Academy of Pediatrics Committee on Infectious Diseases. Intravenous gammaglobulin use in children with Kawasaki disease. *Pediatrics* 1988;**82**:122.
26 Shulman ST. Management of Kawasaki syndrome: a consensus statement prepared by North American participants of the third international Kawasaki disease symposium, Tokyo, Japan. 1988 *Pediatr Infect Dis J* 1989;**8**:663–5.
27 Dajani AS, Taubert KA, Gerber MA, *et al*. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;**87**:1776–80.
28 Rowley AH, Shulman ST. What is the status of intravenous gammaglobulin for Kawasaki syndrome in the United States and Canada? *Pediatr Infect Dis J* 1988;7:463–6.
29 Gentles TL. Clarkson PM, Trenholme AA, *et al*. Kawasaki disease in Auckland, 1979–1988. *N Z Med J* 1990;**103**: 389–91.
30 Akiyama T, Yashior K. Probable role of streptococcus pyogenes in Kawasaki disease. *Eur J Pediatr* 1993;**152**:82–92.
31 Burns JC, Mason WH, Glode MP, *et al*. Clinical and epidemiologic characteristics of patients referred for evaluation of possible Kawasaki disease. *J Pediatr* 1991;**118**:680–6.
32 Reller M, DeCristofaro J, Schwartz DC. Coronary aneurysm in a patient with atypical Kawasaki syndrome and a streptococcal infection. *Pediatr Cardiol* 1984;**5**:205–8.
33 Anderson DG, Warner G, Barlow E. Kawasaki disease associated with streptococcal infection within a family. *J Paediatr Child Health* 1995;**31**:355–7.
34 Hoare S, Albinum M, Cant AJ. Overlap between Kawasaki disease and group A streptococcal infection. *Pediatr Infect Dis J* 1997;**16**:633–4.