Clinical aspects of 100 patients with Kawasaki disease

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Abstract

We report 101 episodes of Kawasaki disease in 100 patients seen over a 12 year period. A total of 35 patients had cardiac involvement ranging from pericardial effusion to coronary artery aneurysms with ischaemic complications, which resulted in death in one patient. Laboratory investigations showed leucocytosis, thrombocytosis, and a raised erythrocyte sedimentation rate to be common features and the first two variables were significantly associated with cardiac involvement. Treatment regimens changed over the study period. Aspirin was used in most patients often in conjunction with dipyridamole and from 1986 intravenous immunoglobulin was given routinely to those patients seen early in the illness. Additional therapeutic measures in individual patients included prostacyclin, heparin, streptokinase, and plasma exchange/exchange transfusion. Attention is drawn to the uncertainty of the long term cardiovascular consequences in the light of adults reported with premature atherosclerotic lesions of similar appearance to those seen in Kawasaki disease.

Mucocutaneous lymph node syndrome or Kawasaki disease was first described in 1967 by Tomisaku Kawasaki.¹ This systemic vasculitis of childhood has since affected over 80 000 children in Japan. Its importance is the predilection for involvement of the coronary arteries in about 20-40% of cases, which in a small number may lead to coronary thrombosis, myocardial infarction, and death.

In the United Kingdom, as in other European countries and the United States, far fewer cases have been reported than in Japan. The British Paediatric Surveillance Unit (BPSU) started an active reporting system in 1986 and since that time the number of reports have increased but still only to about 70-90 cases per year.² Although this may be due to racial influences, it may in part also be due to a lack of awareness of the disease coupled with the absence of a diagnostic laboratory test.

In view of the relatively large number of patients with Kawasaki disease referred to this hospital and the lack of published data on the disease from the United Kingdom we have undertaken a retrospective review of our experience. Clinical details were obtained from the case files. In the majority the data was adequate but in some patients who had been referred only for echocardiography details were occasionally limited.

Patients and methods

PATIENTS

One hundred patients were referred to the Hospital for Sick Children over a 12 year period from 1977 to 1989. One patient had a relapse seven years after the initial episode, therefore 101 cases were analysed. Eighty children had been referred for management and advice and a further 20 for echocardiography only.

The diagnosis of Kawasaki disease was normally based on the presence of five of six of the established clinical criteria (table 1) or the presence of four criteria if coronary artery aneurysms were demonstrable. In some patients referred for echocardiography only, a diagnosis of Kawasaki disease had been made on apparently good evidence at the referring hospitals and despite the relatively inadequate clinical history these patients were included in the analysis.

There were 56 boys and 44 girls giving a ratio of 1.27:1. The age range was 0.25-11.9 years with a mean of 2.83 years and median of 2.2 years. The peak incidence occurred in the 0-1 year age group (figure).

The annual incidence increased over the period of study but there were no major fluctuations from year to year. More cases were admitted in the spring and early summer and there was an ethnic preponderance of Oriental and Afro-Caribbean relative to their presence in the general population (table 2).

Of the diagnostic criteria (table 1) fever of more than five days' duration was present in

Age at presentation with Kawasaki disease.

Table 1 Diagnostic clinical criteria for Kawasaki disease

- (1) Presence of fever for >5 days
- (2) Mucosal inflammation including sore/cracked lips, injected pharynx, or strawberry tongue
- (3) Lymphadenopathy
- (4) Polymorphous exanthema
- (5) Bilateral conjunctivitis
- (6) Characteristic changes in the peripheries: erythema of the palms and soles, desquamation of the fingers and toes, and peripheral non-pitting oedema

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Table 2 Nationality of patients

	% Cases of Kawasaki disease	% In United Kingdom
White	54	
Oriental	12	1
Afro-Caribbean	21	2
Indian subcontinent	6	4
Other	6	
Unknown	1	

Table 3 Symptoms

	No of cases
Fever	100
Rashes	99
Lymphadenopathy	98
Mucosal inflammation	88
Peripheral changes	84
Conjunctivitis	80

nearly all cases. Next in frequency came polymorphous exanthemata most often a morbilliform maculopapular rash with widespread involvement of the trunk and extremities. Lymphadenopathy was common, including patients in whom enlarged nodes were noted but not necessarily measured. Changes in the mucous membranes involved injected and dry cracked lips in addition to pharyngeal injection and strawberry tongues. Peripheral extremity manifestations included peripheral oedema and erythema and in most cases there was a history of desquamation of the fingers and/or toes. Conjunctivitis was noted in 80 cases and was bilateral and non-purulent (table 3). Fifty four cases satisfied six criteria, in 30 five were met, in 15 four, and in one case only three diagnostic criteria were recorded.

CARDIOVASCULAR FINDINGS

A total of 35 cases had cardiac manifestations including 18 cases who had coronary artery aneurysms (most, but not all of these patients have had their coronary artery lesions described in the companion paper³). The non-aneurysmal cardiac complications included dilatation of the coronary artery in 12, pericardial effusion in four, abnormalities seen on electrocardiography suggesting ischaemia in seven, pericarditis in two, myocardial infarction in two, and myocarditis (with raised cardiac enzymes), left ventricular aneurysm, thrombus within aneurysm, mitral incompetence, and cardiac failure in one case each. Cardiac complications occurred more frequently in the younger patients and the median age of those with cardiac involvement was 1 year compared with 2.2 years for the whole group, but there was no preponderance of either sex.

OTHER SIGNIFICANT FINDINGS

In 81 cases in whom more detailed information was available there were a number of other symptoms or clinical findings recorded. These are detailed in table 4.

LABORATORY INVESTIGATIONS

Most patients showed evidence of an acute

Table 4 Other significant findings (n=81)

	No (%) of cases
Irritability	41 (51)
Diarrhoea	27 (33)
Vomiting	18 (22)
Joint pain and tenderness	18 (22)
Preceding upper respiratory tract infection	10 (12)
Hydrops of the gall bladder	9 (11)
Pneumonia	2 (2)
Abnormality on electroencephalography	1 (1)
Raised creatinine	1 (1)
Hypertension	1 (1)

Table 5 Laboratory investigations

Investigation	No of cases studied	Result
White cell count ($\times 10^9/l$)*	89	4.4-49.6 (19.4)
Erythrocyte sedimentation rate (mm in first hour)*	73	14-180 (73)
Platelet count ($\times 10^9/l$)*	93	110-1452 (793)
C reactive protein	28	Raised in 13
Antistreptolysin O titre	40	Raised in 8
Anti-DNAse B titre	27	Raised in 9
Pyuria	70	Present in 16†
Proteinuria	70	Present in 4‡
Cerebrospinal fluid white cell count	20	Raised in 8
Plasma albumin (g/l)*	63	20-45 (29.1)
Aspartate aminotransferase (IU/l)*	58	13-990 (89)
Alanine aminotransferase (IU/l)*	53	10-638 (74)
IgG	33	Raised in 4
IgA	33	Raised in 11
IgM	33	Raised in 12

*Results are range (mean).

†Infected in three; ‡infected in one.

phase response with a rise in their erythrocyte sedimentation rate, white cell and platelet counts, and C reactive protein concentration; however, none of these responses is specific for the disease. The results are shown in table 5.

Autoantibodies were measured in 23 cases. There was a mildly raised antinuclear antibody in two cases and a slightly raised smooth muscle antibody in five patients. Antineutrophil cytosolic antibodies and antiendothelial cell antibodies have been measured more recently in patients with Kawasaki disease and have been reported separately,^{4,5} but both have been shown to be raised in most patients with Kawasaki disease in whom they were measured. Microbiological investigations did not show a consistent infecting organism.

PREDICTION OF CARDIAC SEQUELAE

An attempt was made to see if any of the laboratory variables might predict cardiac involvement. The platelet count was significantly higher in the group with cardiac disease compared with those with no cardiac involvement ($p<0.001$). The white cell count was similarly higher ($p<0.01$) in the group with cardiac disease. There was no significant difference in the erythrocyte sedimentation rate between groups.

Treatment

A wide variety of treatment regimes were used changing as the therapeutic policies altered over the 12 year period. The treatment was aimed at initially decreasing inflammation and inhibiting platelet aggregation and this was achieved predominantly with aspirin and dipyridamole.

Eighty nine cases received aspirin and of these 48 did so in combination with dipyridamole. With the advent of Sandoglobulin (Sandoz) in reducing the incidence of coronary artery involvement,^{6,7} administration of this agent has become standard practice in recent years. Twenty seven cases were treated with Sandoglobulin usually with either aspirin or aspirin and dipyridamole. In 10 cases with ischaemic cardiac disease and/or giant aneurysms prostacyclin was used as an antiplatelet agent and in some severe cases plasma exchange or exchange transfusion (two cases), heparin (three cases), and streptokinase (one case) were used, in a variety of combinations with other drugs. Antibiotics were administered at some time during the acute phase of the disease in 59 and five cases received no treatment.

Outcome and sequelae

The patients have been followed up for a period of up to seven years with a mean of 1.23 years. One patient died after a myocardial infarction at 10 days. One patient relapsed seven years after his initial episode of Kawasaki disease, which had not been complicated by coronary artery involvement. However on the second episode he had appreciable coronary aneurysms, which have persisted for a year.

Many of the patients demonstrated some of the features of Kawasaki disease at times of recurrent 'viral' infections and some children had recrudescence of symptoms while still in the convalescent phase of their initial disease. In addition, one patient developed cerebellar ataxia and two patients complained of chest pain after resolution of the primary illness but neither was found to have evidence of cardiac involvement. Seventy four cases made what was considered to be a complete recovery with no obvious sequelae.

Cardiovascular sequelae, defined as abnormalities present at one month or later occurred in 27 cases (table 6). One patient died during the first month but apart from this child there was a continuing resolution of the cardiac complications. Of eight cases who had been followed up for 2.5 years only one had persistent aneurysms.

One patient relapsed with the full syndrome and severe cardiac involvement. There were no episodes of Kawasaki disease in siblings concurrently, although one of the patients had a sibling who had had the disease several years before.

Discussion

The patients described in this series have similar characteristics and results of laboratory investigations when compared with other larger series in Japan and the United States.^{8,9} The male to female ratio of 1.27:1 was slightly lower than that quoted in the Japanese and American data where the ratio is approximately 1.5:1.¹⁰ The peak age of 0-1 years was similar to the peak age of 9-11 months in Japan.⁹ It is known that atypical cases of Kawasaki disease do occur. The data from the BPSU showed the mortality of the children who satisfied three cri-

teria was substantially higher than those who satisfied four, five, or six criteria.² We therefore did include a few cases that fell into this category.

There were no major epidemics as have occurred in Japan in 1979, 1982, and 1985-6,⁹ and the general increase in the number of cases may in part reflect an increase in the awareness of the disease. Our series showed a tendency to a higher incidence in the spring and early summer in contrast with the more frequent finding of a greater number of cases in the winter and early spring in other reported series.¹¹

Kawasaki disease is known to occur in all races with Oriental people being the most often affected, followed by Afro-Caribbeans, with whites proportionately appearing to be protected. This pattern of distribution was reflected in our group of patients.

Our overall incidence of cardiac complications is slightly higher than that normally quoted,⁹ but in this study we have included complications such as pericardial effusions, which are not necessarily due to coronary artery disease. Our incidence of aneurysms, however, is not dissimilar to other reports in the literature.¹¹ For a more detailed description of the cardiac complications in the group of patients seen at this hospital the reader is referred to a second paper dealing specifically with the cardiological aspects.³ It is clear, however, that the majority of detectable cardiac abnormalities in our population of patients resolved within one to two years. There is debate as to whether these children may be at risk of premature atherosclerosis. There have been reported cases of young adults suffering myocardial infarction who were subsequently found to have coronary artery aneurysms consistent with those found in Kawasaki disease,¹² and in one case a history of a Kawasaki like illness in childhood.¹³ The issue of low dose aspirin treatment for a prolonged period remains controversial and the approach to management of this problem is discussed in the second paper but it is clear that these children need to be followed up long term so that this type of question can be answered.

No major conclusions can be drawn from the results of the various treatment regimes utilised at this hospital due to the changes that have occurred over the years. The findings of Furusho *et al*⁶ and Newburger *et al*⁷ that showed a significant decrease in the incidence of coronary artery disease after the use of immunoglobulin has, however, resulted in this becoming standard treatment for affected children. Due to the hospital's tertiary referral pattern the patients were often started on immunoglobulin treatment rather later in the course of the disease than would have been preferred and this may explain the lack of a striking decrease in the cardiac disease after immunoglobulin treatment. The particular experience in the use of both prostacyclin and exchange transfusion is noteworthy. Prostacyclin is a potent inhibitor of platelet aggregation. In a disease where platelet aggregation is found to occur it may obviously have benefits in preventing the release of vasoactive mediators and thrombotic complications.¹⁴ Prostacyclin's vasodilator

Table 6 Cardiac sequelae present at one month or later (n=27, one case had two sequelae)

	No of cases
Persistent aneurysms	13
Dilatation	10
Left ventricular dyskinesia/left ventricular hypertrophy	2
Pericardial effusion	3

properties are also of use in this disease and no adverse effects occurred in any of the patients in whom it was used. Exchange transfusion may have benefits similar to that of plasma exchange in polyarteritis nodosa¹⁵ or other systemic necrotising vasculitides and thus may have a role in the extremely sick infant.

The aetiology of Kawasaki disease remains unknown. A number of organisms have been implicated but none confirmed. In patients in whom comprehensive microbiological investigation was undertaken no consistent findings emerged. The possible role of retroviruses has been extensively investigated by many groups.^{16 17} However the initial positive findings have more recently been refuted.¹⁸ We also support this lack of positive data having studied some of our recent patients in collaboration with Professor R Weiss and his colleagues at the Institute of Cancer Research and we found no evidence of retroviral involvement (R Weiss, personal communication).

Although the number of cases of Kawasaki disease seen in the United Kingdom is small compared with other areas of the world, the disease still accounts for significant morbidity in the paediatric population and it remains important to continue follow up to establish the long term outlook for these patients.

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