Cardiovascular abnormalities in Kawasaki disease

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SUMMARY Eighteen patients with Kawasaki disease underwent serial, cross sectional echocardiographic examinations to determine the extent and subsequent course of cardiac involvement in this disease. The mean follow up period was 12.3 months. Cardiovascular complications were found in a total of 10 patients (55%). Coronary artery aneurysms were detected in 6 patients (33%), pericardial effusions in two, and one patient had electrocardiographic evidence suggesting inferior myocardial infarction. Coronary artery aneurysms, seen exclusively in infants less than 12 months of age, were found in four to regress over a mean period of 7.5 months (range 1 to 13 months). Electrocardiogram, chest radiographs, and clinical examination were unhelpful in identifying those patients with coronary artery aneurysms. Eight patients (44%) were hypertensive, though only two required treatment. While all patients have survived, serial cross sectional echocardiographs should be performed in children with Kawasaki disease to identify those at risk from potentially fatal complications.

Kawasaki disease is an acute, febrile illness affecting predominantly infants and young children.¹ It is characterised by fever lasting five days or longer, non-purulent conjunctivitis, cervical lymphadenopathy, and changes of the oral mucosa and of the extremities. The cause is not known but the disease is thought to be a manifestation of a systemic vasculitis, probably immune complex mediated, with a predilection for the coronary arteries.² Aneurysm formation and thrombotic occlusions may lead to myocardial ischaemia and sudden death.³ Fatalities have been reported in 1 to 2% of patients with Kawasaki disease and usually occur during the third or fourth week after the onset of the fever.¹ Cross sectional echocardiography, a non-invasive technique, has recently been used to detect coronary artery aneurysms in patients with Kawasaki disease.⁴ We have used this technique as well as clinical criteria including electrocardiography and chest radiographs to determine non-invasively the extent of cardiac involvement and its subsequent course in a group of 18 children with Kawasaki disease.

Patients and methods

We studied 18 consecutive patients who were referred to the Hospital for Sick Children, Great Ormond Street, London between May 1981 and

April 1983 and who satisfied the Japanese MCLS mucocutaneous lymph node syndrome) Research Committee⁵ criteria for the diagnosis of Kawasaki disease. All patients had detailed investigations to exclude other possible diagnoses. The clinical features of the group are summarised in Table 1. The follow up period ranged from three to 26 months (mean 12.3 months). Nine patients have been followed for at least 12 months. A total of 81 cross sectional echocardiograms were performed (mean

Table 1 *Details of 18 patients with Kawasaki disease*

<i>Age* (years)</i>	<i>No</i>
<1	10
1-2	1
2-4	7
<i>Sex</i>	
Boys	12
Girls	6
<i>Ethnic origin</i>	
Caucasian	14
Negro	2
Asian	2
<i>Clinical manifestations (major)</i>	<i>Percentage (%)</i>
Fever (> 5 days)	100
Polymorphous rash	100
Cervical lymphadenopathy	94
Stomatitis	89
Non-purulent conjunctivitis	83
Changes in peripheral extremities	83

*Mean age, 15.3 months (range 4 months to 3 years 3 months).

4.5 examinations per child, range: 2 to 7). Each child had a cross sectional echocardiogram performed on, or soon after, admission and thereafter every one or two weeks while in hospital. The first was performed at a mean time of 16.4 days (range 6 to 34 days) after the onset of symptoms. After discharge all patients were examined at least once during the next three months and at three to 6 monthly intervals thereafter. The electrocardiograms and chest radiographs were taken on admission and repeated subsequently when clinically indicated. If the echocardiogram was abnormal twice weekly electrocardiograms were carried out. Full blood counts including platelet counts were done at least three times each week while the patient was in hospital. Treatment consisted initially of high dose aspirin (50 to 100 mg/kg daily) until the temperature subsided and then either 10 to 30 mg/kg daily or, in later cases, on alternate days for a minimum period of 6 months. All children remained in hospital until the fourth week of the illness at which time the likelihood of cardiac disease developing had diminished. If cardiovascular abnormalities did develop the patients remained in hospital until they were considered stable.

Cross sectional echocardiography. All cross sectional echocardiograms were performed with an Advanced Technology Laboratory mechanical sector scanner using a 3.5 or 5.0 MHz transducer. Each patient had a complete initial evaluation using subcostal, apical, parasternal, and suprasternal cuts. Special attention was paid to the coronary arteries and to left ventricular function in the parasternal short and long axis views. The coronary arteries were initially viewed in the parasternal short axis view and the transducer rotated to the long axis of the appropriate artery so that at least 10 mm and often up to 25 mm of the proximal segment of each was imaged in all patients. A portion of the distal right coronary artery in the right atrioventricular

groove was also examined from the apical four chamber view. Follow up studies were confined to the coronary arteries and left ventricular wall motion in parasternal short and long axis as well as apical four chamber cuts. All echocardiograms were reviewed by one of us (PJR) at the conclusion of the study without knowledge of the identity or clinical status of the patients.

Results

Important cardiovascular complications were found in 10 (55%) of the 18 patients (Table 2). All 18 patients have survived. Coronary artery aneurysms were detected in 6 patients (33%), affecting the proximal portion of the left coronary artery in four patients and both main coronary arteries in two (Fig. 1). In no patient was there isolated involvement of the right coronary artery. The aneurysms were detected during the subacute phase of the illness at a mean time of 21 days (range 15 to 28 days). All occurred in infants who were less than 12 months of age ($P < 0.02$). Most of our patients developed high peak platelet counts but those with aneurysms had much higher values ($910 \times 10^9/l$ to $1250 \times 10^9/l$, mean $1104 \times 10^9/l$) than those without ($380 \times 10^9/l$ to $990 \times 10^9/l$, mean $741 \times 10^9/l$). Only one patient without an aneurysm had a higher platelet count than $900 \times 10^9/l$. In four of the 6 patients with aneurysms maximal thrombocytosis was noted soon after the detection of the coronary abnormalities.

Regression of aneurysms was observed in four patients over a mean period of 7.5 months (range 1 to 13 months) (Fig. 2). In the remaining two patients (cases 9 and 14), aneurysms were still present after 8 months and three months respectively. In two patients who had aneurysms of the left coronary artery, echocardiograms showed persistently reduced motion of the interventricular septum. None of the 6 patients had shown other clinical features to

Table 2 Cardiovascular complications in 10 patients with Kawasaki disease

Case no	Age	Sex	Cross sectional echocardiogram	Electrocardiogram	Cardiomegaly on chest radiograph
1	11 mths	F	Left coronary artery aneurysm	ST segment elevation	+
2	2½ yrs	M	Pericardial effusion	Left axis deviation, LVH	—
4	7 mths	M	Left coronary artery aneurysm	ST segment elevation	—
6	6 mths	M	Pericardial effusion	Inferior infarction, LVH	+
9	6 mths	M	Bilateral coronary artery aneurysms	Normal	+
10	6 mths	F	Normal	Normal	+
11	5 mths	F	Left coronary artery aneurysm	Normal	—
13	5 mths	F	Left coronary artery aneurysm	Normal	—
14*	4 mths	M	Bilateral coronary artery aneurysms	Normal	—
15*	9 mths	M	Normal	Normal	—

*Persistent hypertension.

LVH=Left ventricular hypertrophy.

Fig. 1 Cross sectional echocardiogram (parasternal short axis) showing aneurysms of both main coronary arteries. Ao=cross section of aortic root; LA=left atrium; LCAA=left coronary artery aneurysm; RCAA=right coronary artery aneurysm.

suggest myocardial ischaemia. In the patients in cases 11 and 14 abnormalities of the coronary arteries (dilatation, thickened vessel walls) were recognised before the development of aneurysms—in the latter child during the first week of the illness. Small pericardial effusions that resolved without treatment were seen on echocardiography in two patients. Electrocardiographic and chest radiograph

abnormalities which had been present in 6 patients also resolved. The only exception was the patient in case 6 who presented with cardiomegaly, a raised serum lactic dehydrogenase concentration, and an electrocardiogram suggestive of an inferior myocardial infarction; he has continued to have cardiomegaly on chest radiograph. Serum creatine phosphokinase-MB isoenzyme was not estimated.

Systolic hypertension (systolic blood pressure greater than the 95th centile for age)⁶ was present in 8 patients (44%) during the course of the illness. In 6 patients this was mild, intermittent, required no treatment, and settled soon after the acute phase symptoms resolved. In two patients, however, (cases 14 and 15) blood pressure was persistently raised and has required treatment with beta blockers and vasodilators. Plasma renin and aldosterone concentrations in these two patients were raised. Technetium labelled DMSA scans of the kidneys were normal.

Discussion

The aetiology of Kawasaki disease remains unknown, although an infective hypothesis has been postulated.^{7,8} The diagnosis of coronary artery lesions and the prevention of sudden death are the major issues in the management of these children. Coronary aneurysms have been reported in approximately 20% of patients in Japanese and American series.^{2,9}

Aneurysms usually affect the proximal portion of

		1w	2w	3w	4w	3m	6m	12m	2y
Case	Age								
1	11m			↓	↓	↓	↓	↓	↘ ↘
2	2.5y		↘ ↘		↘ ↘	↘ ↘	↘ ↘		
4	7m		↓	↓	↓	↓		↘ ↘	
6	6m				↘ ↘ ↘ ↘	↘ ↘		↘ ↘	
9	6m			↓	↓ ↓ ↓ ↓	↓ ↓	↓	↓	
10	6m	↘ ↘	↘ ↘	↘ ↘	↘ ↘		↘ ↘		
11	5m		↘ ↘	↓ ↓	↓ ↓	↓	↘ ↘		
13	5m		↘ ↘	↓	↓ ↓ ↘ ↘	↘ ↘			
14	4m	↘ ↘	↓		↓	↓			
15	9m	↘ ↘		↘ ↘	↘ ↘	↘ ↘ ↘ ↘			
		↘ ↘	↘ ↘	↘ ↘	↓	↓			
		Normal		Pericardial effusion		Abnormal		Coronary artery aneurysm	

Fig. 2 Serial cross sectional echocardiographs in 10 children with cardiovascular complications from Kawasaki disease.

the main coronary arteries in this disease¹⁰ and their presence at this site can be reliably detected by cross sectional echocardiography.^{11 12} Using this technique Kato *et al*¹¹ correctly diagnosed 92% of proximal coronary artery aneurysms which had been shown by angiocardiology. Two recent reports have shown the efficacy of modified, subcostal cross sectional echocardiographic cuts in identifying peripheral coronary aneurysms. Among our patients subcostal cuts were performed only on initial studies (see Methods) and when these were reviewed no new aneurysms were found even though most of the cuts described by Yoshida¹³ and Maeda *et al*¹⁴ were available. The later development of left coronary aneurysms or right coronary aneurysms in an area other than that which we routinely imaged cannot be excluded in our patients. Nevertheless, we have shown a high incidence of cardiac complications including aneurysm formation in our group of patients with Kawasaki disease using cross sectional echocardiography. Those patients with aneurysms did not have any clinical, radiological, or electrocardiographic features to suggest their presence.

The particular predilection for the proximal portion of the coronary arteries may be due to the blood supply, which is via nutrient arteries of narrow calibre in the young. If these vessels are affected by severe arteritis diminished blood supply to the walls of the proximal coronary arteries could result.¹⁰ This may be why infants are at greater risk of developing coronary artery aneurysms than older children.¹⁵ We also noted that children who developed aneurysms had the highest platelet counts which sometimes peaked late in the subacute phase after the coronary abnormalities had been detected. The degree of thrombocytosis may therefore reflect basic disease activity and very high values may be a marker of the presence of severe arteritis and increased likelihood of aneurysm formation.

Our findings are in keeping with those of Kato *et al*¹⁶ who showed that aneurysms developed predominantly during the subacute phase of the illness. Regression of aneurysms may occur in as many as 50% of the patients in the first 18 months, and seems to be a characteristic feature of the arteritis in Kawasaki disease.¹¹ In our patients regression of aneurysm was seen to occur on average within 7.5 months. In one patient (case 13)¹⁶ this was observed as early as one month after the onset of the illness.

The disappearance of aneurysms results from a proliferative thickening of the intima and evidence suggests that early treatment with aspirin prevents superadded thrombus formation.¹⁷ It is our current practice to treat all patients with Kawasaki disease with anti-inflammatory doses of aspirin initially and then in lower doses (10 mg/kg) on alternate days to

reduce platelet aggregability. We base this practice partly on the recommendations of Melish² and Hanley *et al*¹⁸ who postulated that low dose, alternate day treatment regimens with aspirin may be sufficient to prevent platelet aggregation without affecting prostacyclin production from endothelial surfaces. The optimum dose of aspirin, however, is still not known.

Hypertension, which has been rarely reported in Kawasaki disease,^{11 19} is not a surprising finding. Cases 14 and 15 both had sustained systolic and diastolic hypertension that required treatment. In view of the raised renin and aldosterone concentrations a renovascular aetiology is likely in these two patients. The mild, intermittently raised systolic blood pressure present in the other 6 children during the early stages of the illness may be a result of the extreme irritability which is a striking feature in patients at this time.

None of our patients underwent coronary arteriography because we feel the marginally increased accuracy is more than outweighed by the potential risk of performing this procedure in infants. Coronary arteriography should be reserved for those with normal echocardiograms but who have other evidence suggestive of myocardial ischaemia or infarction. The patient in case 6 who had a normal echocardiogram but an electrocardiogram suggestive of myocardial infarction may have had an abnormality of a peripheral branch of one of the main coronary arteries but he was lost to follow up before angiography could be arranged.

We recommend cross sectional echocardiographic evaluation of all patients with Kawasaki disease at the time of diagnosis and again at four weeks after the onset of fever. A further study should be done at three to four months. Special attention should be given to patients less than 12 months of age and those who have had a noticeable degree of thrombocytosis. Patients found to have coronary artery aneurysms should be evaluated at least three to six months and long term follow up of *all* children should be carried out to determine whether, as suggested by Kato *et al*,¹¹ there is an increased incidence of premature coronary atherosclerosis. The potential limitations of cross sectional echocardiography in identifying coronary ostial stenosis,¹¹ especially as patients grow older and echocardiographic windows become poorer, should be remembered. The tendency for aneurysms to regress suggests that most patients have a good prognosis. There are reports, however, of myocardial infarction and sudden death occurring some years after the illness has apparently subsided.^{20 21} Persistent hypertension should be sought and treated.

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