Current Paediatrics (2005) **15**, 62–68

Current
PAEDIATRICS

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Complications of Kawasaki disease

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KEYWORDS
Kawasaki disease;
Complications;
Cardiac sequelae;
Gastrointestinal;
Neurological;
Skin;
Renal;
Haematology;
Fever

Summary Kawasaki disease (KD) is a systemic vasculitis and the leading cause of acquired heart disease in the developed world. The most severe, frequent complication of KD is the development of coronary artery involvement, although the introduction of treatment with intravenous gammaglobulin has reduced this problem. In those with a history of coronary artery involvement, long-term follow up is recommended. Kawasaki disease can be a widespread vasculitis affecting many systems, and some of the other recognized complications are discussed, including those affecting the skin, nervous system, gastrointestinal tract, musculo-skeletal system, kidneys, lungs, eyes and haematological effects. About 10–30% of children fail to respond to intravenous gammaglobulin and alternative management strategies including the use of steroids are discussed.

Practice points

- Kawasaki Disease is the commonest cause of acquired heart disease in the developed world
- Early treatment with intravenous gammaglobulin (IVIG) reduces the incidence of coronary artery aneurysms (CAA)
- Atypical/incomplete KD should be considered in the absence of the full standard criteria, particularly in a child with a fever for 5 days
- KD is a multi-system disease and unusual symptoms may be part of the systemic illness
- In 10–30% of children the fever is unresponsive to IVIG. Steroids may play a role in management but should be discussed with an expert in KD

Introduction

Kawasaki disease (KD) is an acute febrile vasculitis, which was first described by Tomisaku Kawasaki in 1967 in a report of 50 children with fever, rash, conjunctivitis, cervical lymphadenopathy and erythema of the palms and soles of the feet. Since then over 170 000 children have been diagnosed in Japan, and KD is the leading cause of acquired heart disease in children in the developed world.

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doi:10.1016/j.cupe.2004.09.002

Table 1 Diagnostic criteria for Kawasaki disease.

Fever of at least 5 days duration plus four of the following features:*
Bilateral conjunctival injection
Polymorphous exanthem
Changes in the lips and oral cavity
Cervical lymphadenopathy (>1.5 cm)
Changes in the extremities:
Erythema of the hands and feet
Swelling of the hands and feet
Desquamation
Other diseases must be excluded

*Incomplete KD may be diagnosed with at least two of these features, no other diagnosis and laboratory features supportive of severe inflammation or coronary artery aneurysms.

KD can occur at any age, but about 85% of cases occur in children under the age of 5 years. It is most common in Japan and Japanese Americans in whom the incidence is 134–135 per 100 000 children under the age of 5 years. In the UK the incidence is reported to have doubled over the past 10 years to 8.1 per 100 000 children under the age of 5 years.[1]

The diagnosis (Table 1) of KD is based on the clinical features of fever >38.5 °C for at least 5 days together with four of five other features, including: rash; bilateral conjunctival injection; changes in the peripheral extremities; lymphadenopathy; and oral changes (Fig. 1). If CAA are present, only three other features are required.

'Atypical' or 'incomplete' KD is used to describe those children who do not meet the full criteria for the disease but whose symptoms are consistent with KD and are not explained by any other diagnosis. Sometimes these patients are atypical at presentation but subsequently develop more features consistent with typical KD.

There are many other clinical features of KD which are variably seen in individual cases. Post-mortem studies have shown that any part of the arterial tree may be affected. Figure 2 shows a patient with an axillary aneurysm, a less common site to be affected as significantly as this. Clinical features affecting many systems are documented in the literature and may be present at diagnosis or during the development of the illness.

Complications

Cardiac

The commonest and potentially most life threatening complication of KD is the development of CAA. In untreated KD, up to 25% of patients develop CAA (Fig. 3), and in a small number this may result in coronary thrombosis (Fig. 4), myocardial infarction and death. Most aneurysms will develop within 6–8 weeks from the onset of the illness. Other cardiac complications include myocarditis, pericarditis, congestive cardiac failure, pericardial effusion, mitral or aortic insufficiency and arrhythmias. In a study of KD in the UK between 1980 and 1988, coronary arterial lesions were seen in 28% and persisted in 23% of patients, most commonly in the younger children.[2] Mortality has been reported to vary between 0.08% and 3.7% in Japan and the UK respectively.[3] This is in part due to the varying recognition of the disease and also to advances in treatment.

The introduction of the use of intravenous gamma-globulin (IVIG) in the first 10 days of the illness has dramatically reduced the incidence of coronary artery disease to approximately 2%. A recent Cochrane Review of the effect of IVIG on the incidence of CAA showed that there was a significant reduction in the development of CAA when compared to treatment with placebo at 30 days (RR 0.74, 95%CI 0.61–0.9).[4] If children with CAA at onset were excluded, the benefit was greater. At 60 days there was trend towards benefit of treatment with IVIG.

Long-term cardiac sequelae

In a multi-centre follow-up study in Japan, information on cardiac status was obtained in 1594 patients who had presented in 1996.[5] Of the 1338 in whom follow-up data was available, 136 (10.3%) had cardiac sequelae at 1 month and 4.2% at 1 year. The prevalence of sequelae was greater in males than females and in those &1 year and >5 years, and was also associated with a low albumin. Ten of the 1594 patients had giant aneurysms, and three died, two due to myocarditis and one to sudden infant death syndrome (SIDS).

Overall, about 50% of aneurysms regress within 5 years. Mild dilatation (3–4 mm) regresses within 2 years, and 80% of those with moderate dilatation (4–8 mm) regress within 5 years. However, giant aneurysms (>8 mm) are unlikely to resolve, and many progress to stenosis or complete obstruction within years of the initial diagnosis. The main cause of death in KD is myocardial infarction secondary to thrombosis of an aneurysm or stenosis (Fig. 5). In a large Japanese study of 195 patients who had experienced a myocardial infarction, the first event occurred in the first year after the disease in 72.8% of the children. The mortality rate was 22% from the first myocardial infarction. Of the 16% who had a second myocardial infarction the mortality rate

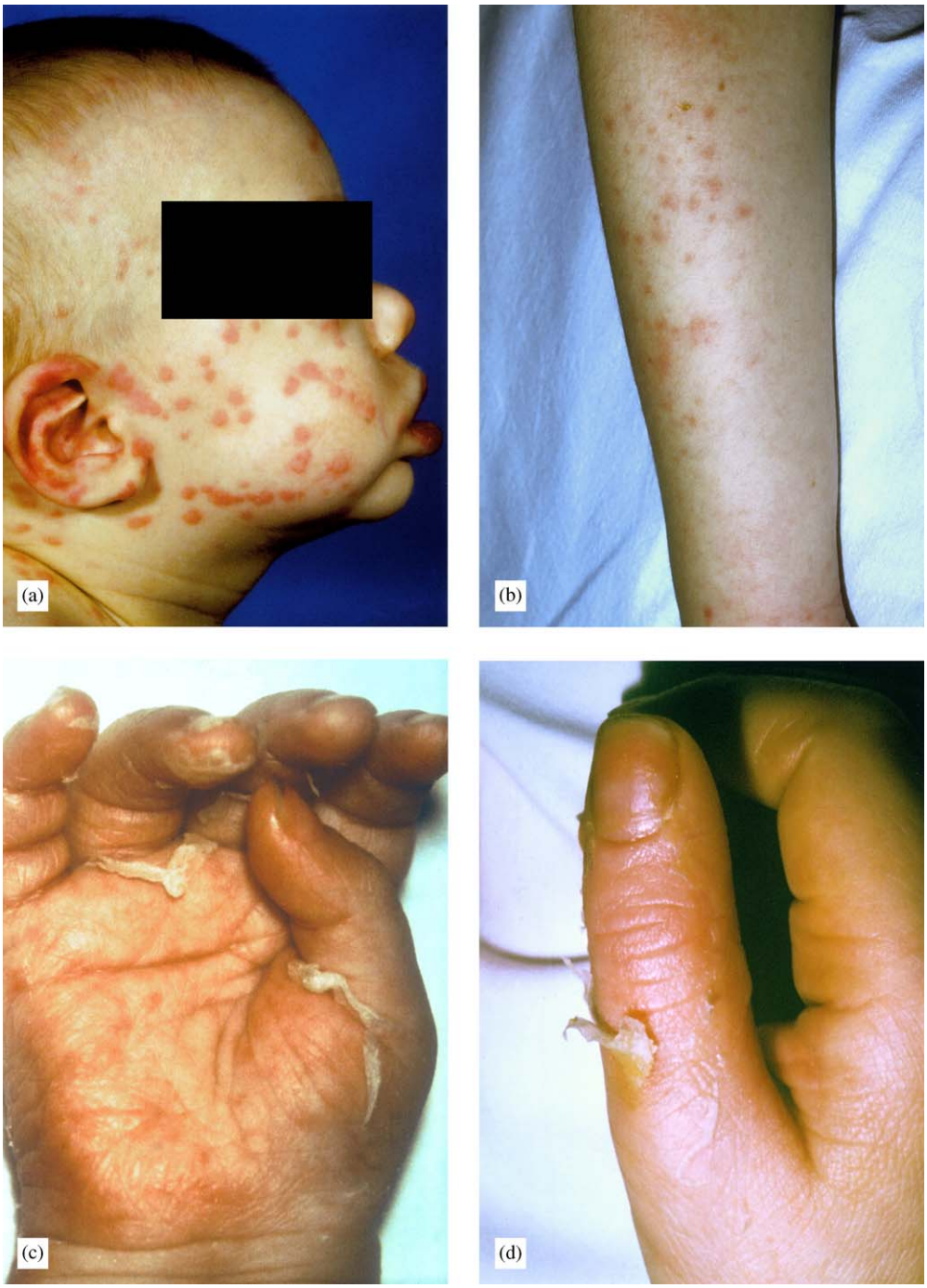


Figure 1 (a) Rash of Kawasaki disease and red lips. (b) Rash of Kawasaki disease. (c) Desquamation of finger tips in Kawasaki disease. (d) Desquamation of finger tips in Kawasaki disease.

was 62.5%.[6] In children with significant heart disease, follow-up with stress tests and myocardial imaging may identify those who need coronary angiography and potential surgical intervention.

There is now evidence that even in those whose aneurysms have regressed there is persisting abnormal vascular wall morphology and vascular dysfunction. In spite of normal angiographic appearances, ultrasound may demonstrate intimal thickening and decreased pharmacological dilatation.[7] Therefore, it is suggested that these patients should be advised to avoid other risk factors for atherosclerosis and to have life-long cardiological follow-up.

In children in whom there have not been any obvious cardiac abnormalities in the acute phase,

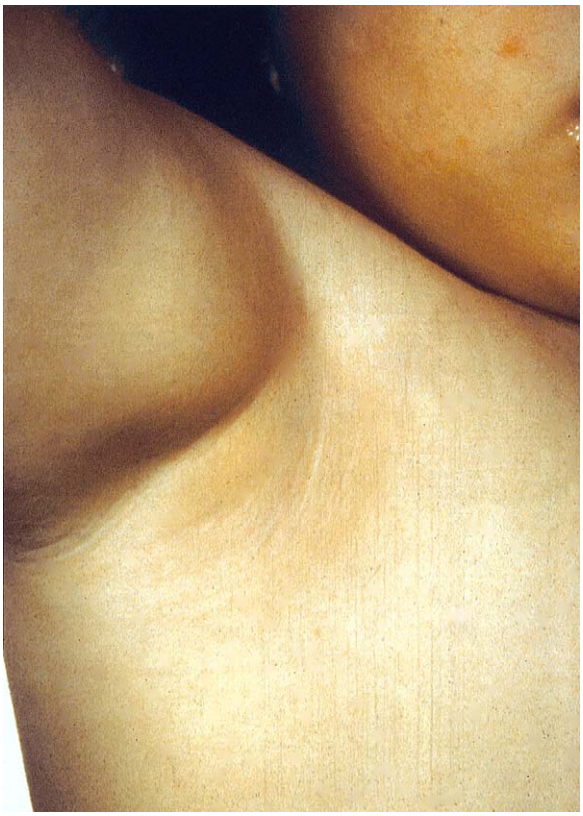
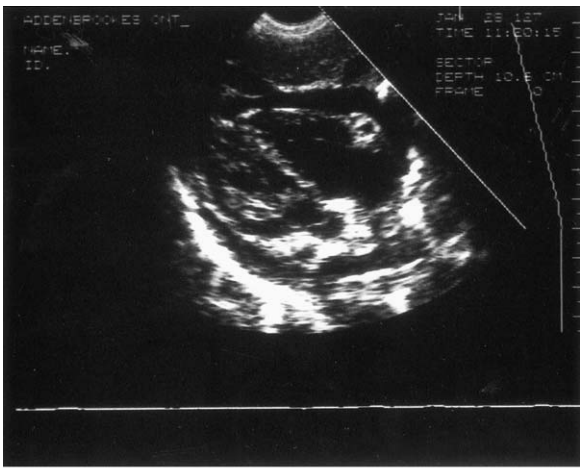


Figure 2 Axillary aneurysm in Kawasaki disease.



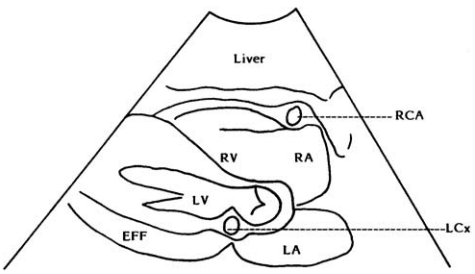


Figure 3 CAA in Kawasaki disease (EFF=effusion, RCA=-right coronary artery, LCX=left circumflex artery, RA=-right atrium, LA=left atrium, RV=right ventricle, LV=left ventricle).

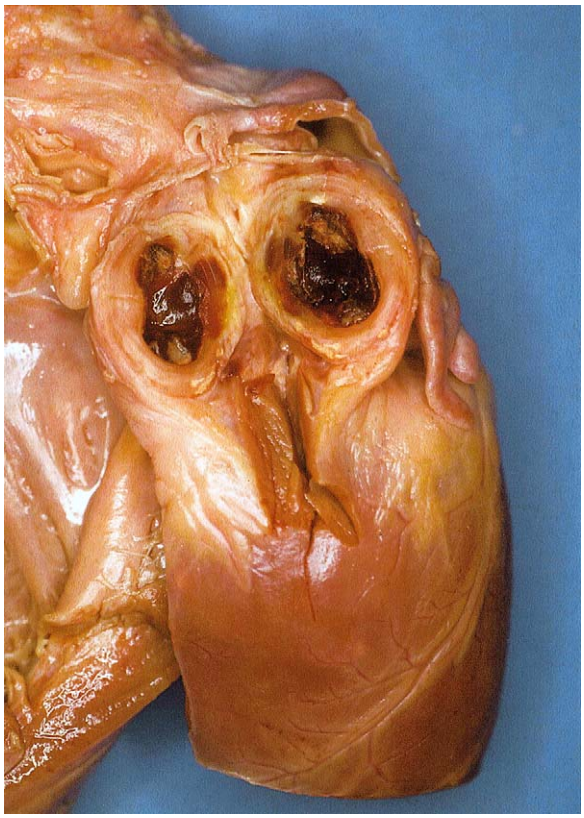


Figure 4 Large coronary artery aneurysm and thrombosis.

Table 2 Treatment of Kawasaki disease.

1. Intravenous gammaglobulin (IVIG) 2 g/kg as a single infusion over 12 h
2. Aspirin 30–50 mg/kg/day in four doses (in USA 80–100 mg/kg/day in four doses is recommended) until afebrile for 2–3 days
3. Aspirin 3–5 mg/kg/day once daily (anti-platelet therapy) for 6–8 weeks minimum

If fever persists after 48 h or recrudescence of fever within 2 weeks—discuss with expert
Possible interventions include:

1. Second dose of IVIG 2 g/kg
2. Third dose of IVIG 2 g/kg *or*
3. Methyprednisolone 30 mg/kg daily for 3 days or prednisolone 2 mg/kg/day orally and tailored based on clinical/inflammatory marker improvement
4. (Cyclophosphamide, Cyclosporin, plasmapheresis and monoclonal antibodies to TNFalpha have been reported)

the longer-term risks are unclear. In a study of post-mortem findings of patients who died of unrelated causes, histological findings of intimal thickening and fibrosis, as seen in adult onset arteriosclerosis, were found. Longer-term studies are required to

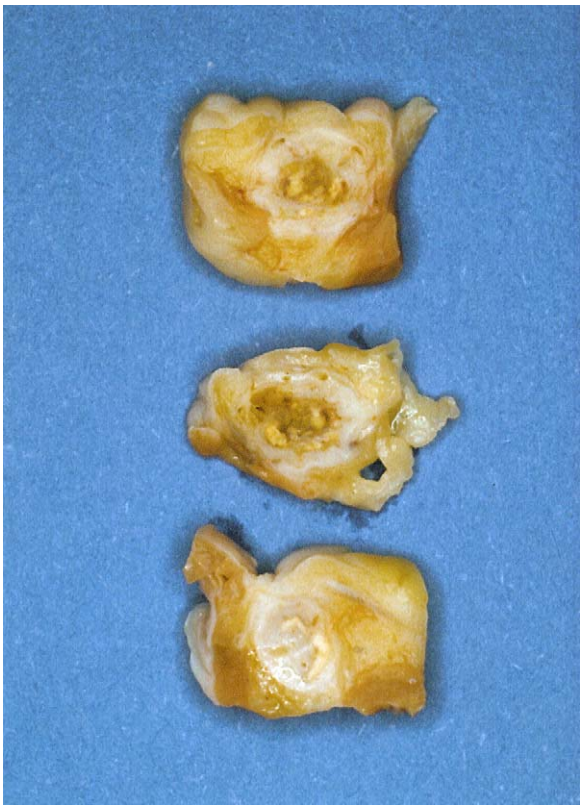


Figure 5 Occluded coronary artery from patient who died of acute myocardial infarction.

determine the clinical cardiac outcome in order to make recommendations for follow-up in those who have not had overt cardiac disease in the initial illness.

Treatment of those with persistent coronary artery abnormalities is primarily with low dose aspirin, 3–5 mg/kg/day, as an anti-thrombogenic agent. Other anti-platelet agents such as dypiridamole, with or without anticoagulation with warfarin, have also been used. In acute myocardial infarction, thrombolytic agents such as streptokinase have been given either intravenously or intracoronary with some success. Surgery has been used in children with persisting stenoses causing ischaemia. Internal mammary artery grafts have been successful, particularly in the older children, with a survival rate of 98.7% at 8 years postoperatively being reported.[6]

Gastrointestinal

Diarrhoea, vomiting and abdominal pain are relatively common findings in KD together with hydrops of the gall bladder. Hepatic dysfunction, with raised liver enzymes, is also well recognized, while jaundice is less common. Liver enlargement has been reported in 14.5% of patients.

An acute surgical abdomen has been described in 4.6% of a series of 219 patients with KD. Nine of these 10 patients had incomplete KD at the time of the acute abdominal presentation, however, 2–4 days later, nine out of 10 had fulfilled the diagnostic criteria. The most common symptoms at presentation were abdominal pain and distension, vomiting, hepatomegaly and jaundice.[8] Late onset necrotizing enterocolitis, possibly due to atypical KD, has also been reported in a 3 month-old infant.

Neurological

Neurological complications are well recognized in KD, occurring in 1–30% of cases. They include irritability, aseptic meningitis, lethargy, transient hemiplegia, cerebral infarction, ataxia, seizures and focal encephalopathy.

Facial palsy is another rare neurological complication, having been reported in 29 patients in the literature by 2003. The reported patients with facial palsy are aged between 3 and 25 months and there is a female preponderance 1.4:1. In a review of the 29 patients,[9] facial palsy was found to be transient, lasting 2 days to 3 months. There was an association with an increased risk of coronary aneurysms, which occurred in 54% of patients, suggesting that facial palsy could be a marker of more severe disease. Histopathological studies from postmortem examinations have shown neuritis and ganglionitis of cranial and peripheral nerves, aseptic choriomeningitis and leptomeningitis. It has been proposed that vasculitis of the vessels supplying the nerves may account for the effect on peripheral nerves.

Cerebral infarction is a rare but reported complication of KD, the incidence of which seems to have fallen with the introduction of the use of IVIG. As it may coincide with the presence of CAA the management may be very difficult.[10]

While late complications of cardiac involvement are well recognized, the implications for more widespread endothelial damage is not well documented. A report of the coincident development of migraine and Raynaud's phenomenon 12 years after KD suggested that this could be due to endothelial dysfunction as a late consequence of KD.

Skin

The diagnostic criteria for KD include polymorphous rashes and changes in the peripheral extremities.

Erythema of the palms and soles occurs in the first week, whereas the typical desquamation begins at about 14–21 days.

Some children develop recurrent skin peeling and in a long-term follow-up of 259 cases of KD, recurrent peeling was documented in 11% of cases, sometimes for several years after the acute illness. In contrast to the initial illness, re-peeling tended to occur within days of the beginning of a mild illness and was thought to be distinct from recurrence of the disease. It occurred more often in those without cardiac involvement and was associated with a high rate of carriage of staphylococcus, suggesting that super antigen release may play a role.[11]

There are a few reports of psoriasis complicating KD. The pathogenesis of psoriasis includes immune activation similar to that seen in KD. It is thought that super-antigens may have a role in the induction and persistence of psoriasis via T-cell activation, including the specific population of T-cells-$V\beta^{2+}$ T lymphocytes, which are also increased in KD.[12]

A clinical sign which appears to be relatively specific for KD is the development of erythema and induration at the site of a BCG immunization. The mechanism is thought to be a cross reaction of T-cells between specific epitopes of mycobacterial and human heat shock proteins.[13]

Renal

Evidence of renal involvement in KD includes proteinuria, haematuria, sterile pyuria and echogenic kidneys. Acute renal failure is rare but has been reported in a few children. Histological findings have included tubulo-interstitial nephropathy, with normal glomeruli, mesangial expansion, negative immunofluorescence and no evidence of vessel involvement. The outcome of patients generally appears to be good, with recovery of renal function.[14]

Musculo-skeletal

While KD affects many organs, muscle involvement is rare, but there have been some case reports. In one such report an 8-month-old boy was found to have raised liver enzymes, AST, LDH, an extremely high creatine kinase and a raised serum myoglobin. A diagnosis of rhabdomyolysis was made. Enzymes improved after defervescence and it was thought that fever may have been the cause of the rhabdomyolysis.[15]

Haematological

Haemophagocytic syndrome (HPS) or macrophage activation syndrome is a rare condition caused by excess activation and proliferation of macrophages. It is usually secondary to a variety of conditions including infections, malignancy, haematological and rheumatological conditions, and has now been reported secondary to KD in a few cases. In a review of five cases, all patients had fever, hepatosplenomegaly and cytopenia, and haemophagocytosis was confirmed on either bone marrow or liver biopsy. All patients had initially improved after treatment of their KD but subsequently deteriorated at about 4 weeks into the illness. Treatment for HPS included etoposide, steroids and cyclosporine.[16] The pathogenetic mechanism is unknown but is thought to be associated with hypercytokinaemia secondary to abnormal T-cell immune-modulation, seen in both KD and HPS.

Other organ involvement

Pulmonary involvement includes the finding of infiltrates on chest X-ray and postmortem findings. A single case report has documented pulmonary dysfunction associated with interstitial lung disease and pleural effusions. Upper respiratory manifestations have included uvulitis and supraglottitis.

Bilateral conjunctivitis is part of the diagnostic criteria for KD and is found in 89–100% of patients. Less commonly, acute iridocyclitis or anterior uveitis are apparent.

Prolonged fever

Standard treatment for KD involves a combination of IVIG and aspirin (Table 2). Although treatment with high dose immunoglobulin has been shown to be effective in reducing fever and the incidence of CAA, there remains a group of 10–30% of children who either fail to remit or develop recrudescence of their fever. Repeat courses of IVIG are successful in some cases but IVIG resistant KD has been reported in 2% of cases.[17]

There was initially concern about the use of corticosteroids for the management of KD, due to the report from Kato et al in which treatment with steroids was associated with a greater risk of developing CAA.[18] However, the patients who were treated with steroids together with aspirin did not have an increased risk of coronary aneurysms, and more recent data have also supported this.

The use of both methylprednisolone and oral corticosteroids has been reported with good effect, predominantly in patients with refractory disease, although other diagnoses should be considered in this situation prior to the institution of treatment.[19,20] Repeat courses of IVIG, however, are usually given prior to the introduction of steroids. For more persistent disease, other potential therapies have included cyclosporin, cyclophosphamide, plasmapheresis and monoclonal antibodies to TNFalpha.[1]

Conclusion

Kawasaki disease is a multi-system disease of unknown aetiology with a characteristic presentation. However, it is a condition that may mimic other systemic diseases with multi-organ involvement and the clinician must investigate appropriately. The mortality is usually associated with the cardiovascular system, but severe involvement of other organs may occur. The very long-term outlook for children with a history of KD remains unknown, and in Japan a national registry, currently with 6500 children entered, has been established to follow these children longitudinally.[1] It will be particularly important to demonstrate whether there is a significantly increased risk of cardiovascular disease in later life, both in those with and without cardiac involvement during the acute illness.

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