Kawasaki disease in children

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ABSTRACT
Kawasaki disease (KD) is an acute self-limiting systemic vasculitis of unknown aetiology. It is the most common cause of acquired heart disease in young children. The intense inflammatory process has a predilection for the coronary arteries, resulting in the development of aneurysmal lesions, arterial thrombotic occlusion or, potentially, sudden death. There is no specific diagnostic test; however, treatment with immunoglobulin and aspirin effectively reduces cardiac complications from 25% to 4.7% in the UK. Inflammation of the myocardium, endocardium or pericardium can occur early in the disease and endothelial dysfunction along with abnormalities of myocardial blood flow may require continuing medication, interventional catheterisation or even cardiac surgery. Several new pharmacological treatments may have important roles to play in managing KD in children and adolescents. This review discusses the history of the disease, the diagnostic challenges, epidemiology, aetiology, pathology, immunopathogenesis, treatment, genetic influences and the long-term cardiovascular sequelae.

Kawasaki Disease (KD) is an acute multisystem vasculitis affecting mainly young children and was described over 40 years ago in Japan by Dr Tomisaki Kawasaki.† Today it represents the leading cause of childhood-acquired heart disease in developed countries.‡ The incidence of KD remains highest globally in Japan (174/100 000 per year of ~5 year olds) and numbers continue to rise, possibly as a result of increased awareness of the condition. There is a recurrence rate of 3.1% and the current mortality rate is 0.04% in Japan.‡ Children aged 6 months to 5 years are most susceptible to KD, with peak incidence occurring in those aged 9–11 months.† Geographical outbreaks and seasonal variation in numbers of cases have been reported.‡

AETIOLOGY
Despite the widely held belief that KD is caused by an infectious agent, there remains considerable controversy over its aetiology. The consensus is that one or more widely distributed infectious agent(s) evoke an abnormal immunological response in genetically susceptible subjects, leading to the characteristic clinical presentation of this disease.

Genetics
A genetic influence is suspected that increases the likelihood of acquiring KD and subsequently the formation of coronary artery lesions. The prevalence varies between different ethnic populations, with people of Japanese origin, independent of their geographical location, being more prone to acquiring KD.†‡§ It has been suggested that genetic polymorphisms disseminated geographically among these populations may influence KD susceptibility, in particular polymorphisms in chemokine receptor genes, in the promoter of the CD14 gene and in some alleles of B and C in the HLA class I genes. The CD40 ligand gene and ITPKC genetic polymorphism are thought to increase the tendency to develop coronary artery lesions.

Superantigens
Recent immunological and microbiological studies suggest a potential role for staphylococcal and streptococcal toxins (superantigens) in the pathogenesis of KD. Superantigens, such as those produced by group A Streptococcus and toxic shock syndrome toxin-secreting and exfoliative toxin-secreting Staphylococcus aureus are potent stimulators of T cells in the peripheral blood-bearing specific Vβ receptors. Work by Leung et al suggests that coronary artery lesions arising in acute KD may result from superantigenic stimulation of Vβ2+ T cells, signifying a possible role for this T-cell subset in the pathogenesis of systemic vasculitides and coronary arteritis.

Infectious agents
An infectious agent is strongly suspected in view of both clinical observations and a number of epidemiological features. Pronounced seasonality and clustering of KD cases has been observed in Japan and this, combined with temporal clustering of cases, suggests that KD has an environmental trigger. Seasonality demonstrates a bimodal distribution, with peak incidence in late winter and early spring, with a nadir in October. Weather patterns are also felt to be influential, as correlations exist between periods of low temperature and high rainfall and clustering of KD cases. Thus it seems likely that KD is associated with some widely distributed infectious agent. The coronavirus has been found in serological analysis of bodily secretions in up to 25% of cases of KD, although this is not felt to be the main causative factor. Work by Rowley et al has shown that oligoclonal IgA plasma cells infiltrate coronary arteries and other inflamed tissues in acute KD, suggestive of an antigen-driven response. The antigen appears to localise to cytoplasmic inclusion bodies that are consistent with aggregates of viral protein and associated nucleic acid within ciliated bronchial epithelium and in a subset of macrophages, found in acutely inflamed tissues in patients with KD. These findings again support a response to a previously unidentified, ubiquitous infective agent.
**DIAGNOSIS**

There is no specific diagnostic test available for KD, with the diagnosis based upon the presence of characteristic clinical findings. The American Heart Association criteria, established in 1993, state that patients must have a fever for more than 5 days accompanied by four out of five of the following signs:

- red eyes, bilateral non-purulent conjunctivitis;
- sore erythematous oral cavity, red fissured lips and classically a "strawberry" tongue with protuberant papillae;
- polymorphous maculopapular skin rash;
- cervical lymphadenopathy, usually unilateral and >1.5 cm in diameter;
- erythema and oedema of the hands and feet. Desquamation of the skin is seen to occur during the later stage of the illness.

In contrast, the Japanese criteria use fever as a criterion, rather than a prerequisite. Irritability, possibly secondary to cerebral vasculitis or to the presence of aseptic meningitis, is a common additional finding in children with KD. Mood alterations, behavioural changes, gastrointestinal upset and diarrhea (20%), pain or arthritis affecting large joints (30%), hydrops of the gall bladder (10%) and deranged liver function tests are other reported sequelae of the disease. Alternative diagnoses should always be considered as some children will fulfil all the diagnostic criteria, but have a different underlying illness. The differential diagnoses include toxic shock syndrome, staphylococcal scalded skin syndrome, scarlet fever, viral exanthemas, cerebral vasculitis or to the presence of aseptic meningitis, is a common additional finding in children with KD. Mood alterations, behavioural changes, gastrointestinal upset and diarrhea (20%), pain or arthritis affecting large joints (30%), hydrops of the gall bladder (10%) and deranged liver function tests are other reported sequelae of the disease. Alternative diagnoses should always be considered as some children will fulfil all the diagnostic criteria, but have a different underlying illness. The differential diagnoses include toxic shock syndrome, staphylococcal scalded skin syndrome, scarlet fever, viral exanthemas, juvenile rheumatoid arthritis and infection with adenovirus, coronavirus, measles, parvovirus and rickettsiae.

**Laboratory studies**

Some laboratory findings can prove helpful in ambiguous cases:

- presence of raised acute phase inflammatory markers erythrocyte sedimentation rate, C-reactive protein;
- raised white cell count — neutrophil leucocytosis;
- urine analysis showing white blood cells on microscopy;
- negative viral titres/antistreptolysin-O test/staphylococcal swabs;
- raised platelet count occurring 10 days after the onset of the illness;
- raised transaminases or bilirubin.

**Incomplete KD**

Along with the rising incidence of KD, more children with incomplete clinical features of the disease are emerging. Incomplete KD includes those patients who satisfy only three of the five criteria but can still display coronary artery involvement. Those under 1 year or older than 4 years of age, are more likely to have an incomplete form of the disease. In up to 90% the absent cardinal feature is cervical lymphadenopathy and a rash may not be manifest in 50%. There is some evidence that those with the incomplete form are most at risk of coronary artery sequelae as described below. Thus, increased clinical awareness, early recognition of this disease and prompt treatment are essential.

**TREATMENT**

The main goals of treatment are to reduce the systemic and coronary arteritis and to inhibit platelet aggregation, thereby preventing arterial thrombosis.

**First-line treatment**

The vast majority of children respond promptly to treatment, which consists of an infusion of intravenous immunoglobulin (IVIg) 2 g/kg, administered over 12 h and high-dose aspirin, at 30–50 mg/kg/day in four divided doses. Randomised, prospective clinical trials in the USA in the 1980s established that IVIg was an effective and safe treatment, which reduced the rate of coronary artery lesions. High-dose aspirin is initially used for its anti-inflammatory effect, but after the acute phase the dose of aspirin is reduced to 5 mg/kg/day, and acts as an inhibitor of platelet function. This is continued for 6 weeks if no coronary artery abnormalities are present or longer if the coronary arteries remain abnormal. IVIg treatment ideally should be instituted within the first 10 days of the illness; however, there may be some benefit in giving IVIg even after 10 days if there is evidence of continuing inflammation.

Combination therapy with IVIg and aspirin arrests the immune-mediated necrotising arteritis and alleviates the acute systemic symptoms of inflammation. Treating children with KD with IVIg and aspirin has been shown unambiguously by meta-analysis to reduce the occurrence of aneurysms. A meta-analysis comparing anti-inflammatory doses of aspirin (30–50 mg/kg/day) with IVIg versus very high-dose aspirin (80–120 mg/kg/day) with IVIg reported no significant difference in the incidence of aneurysms between the two groups.

**Second-line treatment**

A proportion of patients will fail to become afebrile despite treatment with IVIg and aspirin. For those for whom this has not been effective, most clinicians would attempt a repeat dose of IVIg at 2 g/kg in order to achieve resolution of the inflammatory process. Thirteen per cent of a large series of patients with KD were found not to respond to initial IVIg treatment; however, only half of these were successfully treated with a second dose.

**Role of steroids in KD**

Rescue treatments for IVIg-resistant KD have included steroids, but a recent multicentre study from the USA concluded that the addition of a single-pulsed dose of IV methylprednisolone to conventional first-line IVIg treatment provided no extra benefit. The failure of corticosteroids to benefit these patients highlights the difference between KD and the other chronic vasculitides, in which corticosteroids are the cornerstone in most treatment protocols.

**Resistant cases**

There are no treatment guidelines for refractory KD. Immunosuppressive agents, including methotrexate, tacrolimus, ciclosporin and antithymocyte globulin have been used in some resistant cases, but there are no large studies to determine the role, if any, of these cytotoxic drugs. Some experimental evidence shows that other anti-inflammatory treatments such as abciximab, an antagonist of the platelet glycoprotein IIb/IIIa receptor, may be effective. Interestingly, in one series, there was a greater regression of aneurysms which had already formed when treated with abciximab. Plasmapheresis has been used in severe cases but now has mostly fallen into disuse.

Production of proinflammatory cytokines during the acute phase of the illness, such as tumour necrosis factor (TNF-α) coincides with the presence of an inflammatory infiltrate within the coronary arteries. If TNF-α effector functions are absent,
inflammation and elastin breakdown in the coronary vessels are eliminated, which supports the growing body of evidence for the use of anti-TNFα therapy—for example, infliximab, in KD.47 48 There may also be a therapeutic role for antioxidants49 or neutrophil elastase inhibitors.50

Adjunctive treatment
It is important to remember that emollient creams for peeling fingers, balms for sore lips and symptomatic treatment are important adjunctive treatment. Many children have diarrhoea or constipation which will need dietary or medical assistance. In addition, the mood changes and behaviour disturbance that may be seen, will require considerate handling or even psychological intervention.27 Patients are advised not to receive active immunisations for 9 months after the treatment for Kawasaki disease, in order that the vaccinations might be effective.

ACUTE CARDIAC SEQUELAE OF KD
The incidence of cardiac sequelae in KD is falling. In the UK, those children who have been treated with IVIg and aspirin have only a 4.7% risk of coronary artery involvement.5 In a Japanese study of 69 382 patients with KD, 10 596 encountered cardiac sequelae and 15.3% of these occurred more than 1 month after the acute illness.51 Risk factors for developing cardiac sequelae included male sex, age <1 year old or >5 years old, C-reactive protein >100 mg/l, white blood count >30 x 10⁹/l,52 or low serum albumin.53 In addition, those who received their drug late, after 6 days of illness, were more likely to develop complications.54 There are well-described cases with aneurysms outside the heart, but this topic is beyond the scope of this article.

A wide spectrum of severity is seen for cardiac sequelae, including coronary artery inflammation (ectasia), coronary artery aneurysms and inflammation of the myocardium or pericardium. Although many children develop cardiac complications of KD, fortunately most of these are minor and resolve without further complication.55 During the first 10 days of the illness, an influx of inflammatory cells is first seen within the vasa vasorum of the coronary arteries. The intense pancardial inflammatory infiltrate diminishes 10 days or so after the onset of fever but fragmentation of the internal elastic lamina and damage to the media result in coronary artery aneurysms.51 56

Dysregulation of angiogenesis is a contributing factor in the vasculopathy related to KD. Neovascularisation occurs in systemic vasculitis as angiogenesis mediators are secreted by inflammatory cells. High expression of circulating vascular endothelial growth factor, which is believed to be an important regulator of angiogenesis, promoting both blood vessel hyperpermeability and macrophage activation, is considered to be involved in the development of coronary artery lesions.57

Coronary artery aneurysms
The above events result in coronary artery ectasia, mild dilatation up to 5 mm across (small aneurysms), moderate dilatation (up to 8 mm across) or giant aneurysms (>8 mm). Healing and fibrosis of the affected coronary arteries is seen later, leading to stenosis formation, particularly in the post-aneurysmal segment of the artery, with the associated risk of coronary thrombosis, myocardial infarction and sudden death.58 Progressive intimal hyperplasia can be seen many years after the initial episode of KD.59 Most small coronary aneurysms resolve completely but giant aneurysms are unlikely to do so.

Giant aneurysms
Giant aneurysms (fig 1) occur in the worst cases, as described above. Occasionally, giant aneurysms may rupture with fatal consequences.60 61 If the larger aneurysms are still present 3 months after the acute illness, treatments with aspirin, dipyridamole, low molecular weight heparin or warfarin may be needed to prevent thrombosis within the aneurysm, thereby reducing the risk of myocardial infarction.

Imaging
Assessment by two-dimensional echocardiography is recommended at 10 days, 6 weeks and 6 months after the acute illness. This should be aimed at detecting or excluding coronary artery aneurysms, intraluminal or mural thrombi, regurgitant cardiac valves, myocardial dysfunction or a pericardial effusion.

Myocarditis
Myocarditis following KD can result in valvulitis and valvular incompetence 1–3 years after the onset of illness which may require aortic or mitral valve replacement. Pericarditis often resolves as the acute phase subsides but may require an emergency pericardiocentesis. Both the atrioventricular (AV)
conducting system and the myocardium can become infiltrated with inflammatory cells, potentially resulting in AV block and myocardial dysfunction, respectively. Inflammation of the endocardium particularly involves the AV valves, and inflammation of the pericardium can lead to a pericardial effusion. It is well recognised that neutrophilic infiltration of the coronary arteries leads to much of the damage recorded on echocardiography. In addition, there is a peripheral blood eosinophilia and eosinophilic accumulation in the walls of the coronary microvessels. Other markers of acute inflammation include increased serum granulocyte colony stimulating factor, which correlates with the coronary artery dilatation, and also matrix metalloproteinases, which may be involved in coronary artery remodelling and neointimal proliferation.

Role of nitric oxide
Nitric oxide (NO) is a substance secreted by vascular endothelial cells and is thought to play a part in vasculitis and aneurysm development in patients with KD. Increased NO secretion has been shown in mice models of KD to be directly involved in aneurysm formation. It has been proposed that the function of nitric oxide synthase (NOS) is abnormal in patients with KD. This led to the belief that perhaps a genetic link existed in the form of NOS gene polymorphisms. However, induced NOS and endothelial NOS gene allele expression was found not to differ in patients with KD with or without coronary lesions.

LONG-TERM CARDIAC SEQUELAE IN KD
In a cohort study of 594 children with acute KD, 146 (24.6%) were diagnosed with coronary aneurysms. By 10–21 years after the onset of the illness, stenosis in the coronary aneurysm had developed in 28 patients. Myocardial infarction occurred in 11 patients, five of whom died. Systemic artery aneurysms developed in 13 patients (2.2%), valvular heart disease appeared in seven (1.2%) and death occurred in 0.8%. A small number of patients with relentless ischaemic heart disease as a result of KD have undergone cardiac transplantation, which is particularly beneficial if there is severe refractory myocardial dysfunction or where revascularisation is not possible.

KD in adulthood
Long-term cardiac consequences include endothelial dysfunction, abnormalities in vessel wall morphology with intimal proliferation and impaired myocardial flow reserve at the site of regressed coronary aneurysms in patients with previous KD. It is not apparent how many of those with coronary artery dilatation that has regressed will develop coronary artery disease in the long term. A proportion of non-atheromatous coronary artery disease, atypical angina and coronary artery stenosis in adults may be secondary to KD in childhood. Abnormal lipid profiles have also been reported following KD. It is recommended that all these patients should be counselled to avoid potential risks for atherosclerosis.

Assessment of myocardial blood flow
Coronary angiography only provides part of the assessment on children or adults late after the initial presentation with KD as it provides little information about microvascular coronary artery flow or ventricular function. Dobutamine stress echocardiography is an effective method for the follow-up evaluation of coronary arteries and may be a useful alternative for screening compared with cardiac catheterisation. Multislice spiral CT imaging allows evaluation of aneurysms and the extent of luminal stenoses, which is required for risk stratification. However, this technique does have the disadvantage of a significant radiation dose, which is not desirable, especially in the very young, who may require repeat evaluation.

Myocardial blood flow and hence ischaemia can be evaluated using 99mTc tetrofosmin scintigraphy where an intravenous dipyridamole stress test of 0.7 mg/kg is used followed by a single-photon CT, 30 min after injection of 99mTc. In a study involving 86 patients with KD (20 with coronary artery stenosis, 37 with aneurysms but no stenosis and 29 with normal coronaries), 18 of those with significant coronary artery stenosis (>75%) were found to have regional myocardial ischaemia.

Coronary artery Doppler registration can be used to assess coronary flow volume reserve (CFVR). Transthoracic Doppler echocardiography (TTDE) has been shown to be effective in confirming that CFVR is significantly less in stenotic coronary blood vessels than in aneurysmal or normal coronary vessels (p<0.0001). A peak and mean CFVR of <2.0 predicted significant coronary artery stenosis as confirmed by coronary angiography. CFV and CFVR measured non-invasively using TTDE have been shown to accurately reflect the invasive measurement of these parameters using Doppler guidewire methods.

The use of MRI with three-dimensional NAV correction may be better than angiography at assessing coronary arteries, although this has not yet been fully assessed. In young children there is a problem of limited resolution. However, there is the obvious advantage of avoiding ionising radiation. Cardiac magnetic resonance angiography (CMRA) allows serial evaluation of the distribution and size of aneurysms. TTDE may be adequate initially but as children grow, visualising the coronary arteries becomes progressively more difficult and the TTDE images become insufficient. Three-dimensional CMRA can thus provide a non-invasive alternative to TTDE in older children, but more multicentre randomised controlled trials are needed to define precisely the role of CMRA in assessing coronary artery disease.

The use of intravascular ultrasound scanning has been shown to be safe and effective for use in children as assessing coronary artery wall pathology is valuable as it is more sensitive than angiography in detecting vessel wall disease and can identify histopathological features missed by angiographic techniques.

Intervention for myocardial ischaemia
Coronary artery bypass grafting using the pedicled internal thoracic artery, balloon angioplasty, stent insertion, rotational ablation and transluminal coronary revascularisation have been performed in small numbers of severely affected patients with some success, especially in severely stenotic or calcified coronary arteries. In one study, cardiac catheter intervention was performed in 23 patients with KD, four underwent percutaneous balloon angioplasty, seven underwent stent insertion, 10 had percutaneous transluminal coronary rotational ablation (PTCRA) and two had PTCRA with stent insertion; 91% of lesions were dilated successfully. One patient required immediate coronary artery bypass grafting but during the following 3–4 years 13/15 patients needed no more interventions. The optimal timing for intervention is not clear but it should be performed when there is evidence of exercise-induced ischaemia secondary to a stenosis. It is less clear in those children who have lesions with aneurysmal formation but who have no ischaemia on exercise testing.
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