Kawasaki disease: recent advances

It is now 20 years since Dr Tomisaku Kawasaki first reported a series of Japanese children with an illness he called 'acute febrile mucocutaneous lymph node syndrome', but which is now more commonly referred to as Kawasaki disease. The disorder has since been recognised to be an important and relatively common childhood illness, occurring worldwide and with a greatly increased prevalence in Japan. The association of Kawasaki disease with coronary artery aneurysms, coronary thrombosis, and myocardial infarction has made the disorder an unusually worrying one and has led to considerable efforts to establish its cause.

In the past few years there have been exciting advances in the understanding of the epidemiology, pathogenesis, clinical spectrum, and treatment of Kawasaki disease. The purpose of this article is to review briefly some of these important advances, which are of relevance to paediatricians in this country.

**Epidemiology**

Detailed epidemiological studies on Kawasaki disease have been undertaken in many countries. In Japan, where over 80,000 cases of the disease have been reported, the large number of cases and widespread public awareness of the disorder have made possible very accurate documentation of its epidemiology. The disease occurs in epidemics every three years, with peaks in 1979, 1982, and the winter of 1985/86. During these epidemics cases were reported in Japan at a rate of 750 per month and in the interepidemic periods 150–200 cases were reported each month. The epidemics spread in wave like fashion with peaks occurring sequentially in different regions of the country over a period of months. Children aged 6 months to 5 years of age were predominantly affected, with the peak incidence being in children 9 to 11 months of age. Similar epidemics and clustering of cases has been observed in studies in the USA, Canada, and Europe. Despite the obvious epidemic nature of the disease, person to person transmission has not been observed, and secondary cases occurring in contacts of affected patients are extremely rare. Kawasaki disease occurs in siblings of affected patients more frequently than in the general population (2% v 0·19% in Japan), with the highest incidence being in siblings under 2 years of age in whom 8–9% develop the illness. Over 50% of affected siblings develop the illness within a few days of each other suggesting common exposure rather than secondary transmission. The occurrence of epidemics, the specific age group affected, and wave like spread of the epidemic strongly suggests that Kawasaki disease is caused by an infectious agent. However, in view of the lack of secondary cases, the agent responsible must be either one of low communicability, or one which only causes the complete clinical picture of Kawasaki disease in a small proportion of affected patients.

**Family studies**

The possibility that Kawasaki disease represents an unusual reaction to common infectious insults has been investigated by attempting to define a genetic basis for the disorder. Early reports of an association of Kawasaki disease with HLA-BW22 or BW54 have not been confirmed in subsequent studies. Persuasive evidence against a genetic basis came from twin studies, in which monozygotic twins in Japan showed no increased concordance for the disorder over dizygotic twins. Although a genetic basis for the disorder seems unlikely, American children of Japanese descent have a significantly increased risk of the condition as indeed do children of Japanese families in the UK. This together with the high incidence in Japan may indicate a racial predisposition.

**Aetiology**

The clinical features of an acute self limited febrile illness with rash, mucous membrane involvement, lymphadenopathy, and leucocytosis, together with the epidemiological features, suggest an infectious aetiology. However, the failure to identify a causative organism using conventional culture and serological techniques, and the lack of response to antibiotics indicates that the disorder is probably not due to any known bacterial or viral pathogen. Early reports documented rickettsia-like bodies on electron microscopy of lymph nodes from patients with Kawasaki disease, but these observations were not confirmed by others. Similarly an association between house dust mite exposure and Kawasaki disease has not held up to closer scrutiny. Epidemiological evidence linking Kawasaki disease to recent carpet shampooing, an activity that may aerosolise mites or mite associated organisms, was also not substantiated in more recent studies.

In 1983, Kato et al reported isolation of a variant strain of *Propionibacterium acnes* from blood cultures taken early in the illness. *P acnes* is a normal skin commensal which does not usually require any special techniques for its isolation.
The failure of other workers to isolate this organism from children with Kawasaki disease led to some scepticism about its possible role in the disorder. However, Kato and his colleagues have more recently reported that the strains of \( P\) acnes isolated from patients with Kawasaki disease produce an unusual cytotoxin not commonly produced by strains isolated from other sources. The possibility that Kawasaki disease is caused by a toxin elaborated by what are normally commensals or commonly harboured pathogens of low virulence is not without precedent. Staphylococcal toxic shock syndrome, scarlet fever, and the scalded skin syndrome are examples of toxin induced disease which have obvious clinical similarities to Kawasaki disease. The toxins that cause the staphylococcal and streptococcal toxic shock syndromes are now known to belong to a family of enterotoxins which are produced by a variety of different strains of bacteria. These toxins have a common mode of action, binding to specific V-beta regions of the T cell receptor in conjunction with major histocompatibility complex class 2 antigens and acting as superantigens to induce T cell proliferation and cytokine release. As will be discussed below, the immunological findings in Kawasaki disease are similar to those which are induced by the family of enterotoxins, and this, together with the clinical similarities to known enterotoxin disease, raises the possibility that a similar toxin may cause Kawasaki disease.

The association of Kawasaki disease with abnormalities of cellular immunity led to speculation that the disorder might have a retroviral aetiology. In close succession Shulman and Rowley in Chicago, and Burns et al in Boston, reported detection of reverse transcriptase activity in culture supernatants of lymphocytes from patients with Kawasaki disease. Reverse transcriptase is the enzyme which synthesises DNA from an RNA template and is the enzyme characteristically produced by retroviruses. These reports raised the exciting possibility that Kawasaki disease may be yet another disorder to emerge from the 'Pandora's box' of retrovirology. With the current interest in AIDS and retrovirology in general this possibility has stimulated an enormous amount of interest. The epidemiological features of Kawasaki disease would be unusual for a retroviral infection because most known retroviral induced illnesses have prolonged incubation periods and cause chronic and persistent illness rather than the acute self limited illness that is seen in Kawasaki disease. Furthermore a number of more recent studies have failed to identify evidence of a retroviral infection, and it now appears likely that the reverse transcriptase activity detected by Shulman and Rowley and Burns is not specific for viral reverse transcriptase but may instead be due to cellular polymerases.

Pathogenesis
Attempts to understand the pathogenesis of Kawasaki disease have focused on the mechanisms causing the major pathological feature, a vasculitis affecting small and medium sized blood vessels, not only in the coronary circulation but in many other organs of the body. The vasculitis, with endothelial cell necrosis, leucocytic infiltration into the media and adventitia of arteries and venules, and medial disruption, often coincides with dilatation of the blood vessel and intraluminal thrombosis. A number of cellular and humoral immunological abnormalities have been documented during the acute phase of Kawasaki disease. These include deficient T8 positive suppressor/cytotoxic T cells, increased T4 positive activated helper T cells bearing HLA-DR surface antigens, and grossly increased numbers of B cells spontaneously secreting IgG and IgM. Immune complexes have been detected in the circulation two to four weeks after onset of the disease in several studies. Our own studies documented that IgG immune complexes detectable in the circulation of patients with Kawasaki disease were able to induce platelet activation and release of vasoactive mediators. Furthermore there appeared to be an association between the presence of immune complexes and the characteristic thrombocytosis occurring in the second and third week of the illness. Raised plasma concentrations of the cytokines interleukin-1 and tumour necrosis factor and spontaneous in vitro production of cytokines by T cells from patients with Kawasaki disease have also been documented.

The presence of vasculitis has focused the attention of several workers on the mechanisms of endothelial injury. Leung et al demonstrated endothelial cell toxicity of Kawasaki serum for cultured endothelial cells treated with interferon gamma and activation of endothelial cells to express adhesion molecules. In studies conducted at the Institute of Child Health, London, antienothelial cell antibodies as well as antineutrophil antibodies have also been shown to be present. Although the precise pathophysiological sequence involved in the pathogenesis of the vascular damage is far from clear, it seems likely that activation of inflammatory pathways may contribute to the vascular damage and this may offer several sites for therapeutic intervention.

Prognosis
While the aetiology and pathogenesis of Kawasaki disease remain incompletely understood, the clinical spectrum of the disorder and its long term prognosis and treatment are becoming increasingly well defined. Coronary artery aneurysms are demonstrable echocardiographically in 20% to 40% of patients during the acute phase of the disease and 10% to 20% have demonstrable aneurysms during convalescence. Most of the aneurysms appear to regress (at least echocardiographically) during the first year or two after the acute illness. However, a significant number of patients have persistently demonstrable abnormalities for several years. The mortality for coronary artery thrombosis in the acute and early convalescent phase is about 1%. A significant number of patients also have asymptomatic myocardial infarction. Patients with chronic myocardial ischaemia caused by coronary artery stenosis occurring during the healing of a previous aneurysm are increasingly recognised.

The long term prognosis for patients with coronary artery abnormalities who recover from the acute illness is not yet known. An important question is whether patients whose coronary arteries have been damaged by Kawasaki disease will have an increased risk of myocardial infarction in later life. A study of children dying of unrelated causes, who were known to have had Kawasaki disease previously, confirmed that histological abnormalities were still present in the coronary arteries several years after the acute illness.

Diagnostic criteria for Kawasaki disease
(A) Fever of five or more days duration
(B) Presence of four of the following five conditions:
   (1) Bilateral conjunctival injection
   (2) Changes in the mucous membranes and upper respiratory tract, such as injected pharynx, dry cracked lips, strawberry tongue
   (3) Changes of the peripheral extremities including oedema, erythema, desquamation (may occur later)
   (4) Polymorphous rash
   (5) Cervical lymphadenopathy
(C) Exclusion of: staphylococcal and streptococcal infection, measles, leptospirosis, and rickettsial disease

*One of these is sufficient.
Note: in the presence of coronary artery aneurysms detected echocardiographically (A) plus three of the four criteria in (B) is diagnostic.
The abnormalities included thickening and hyperplasia of the intima and media of the artery. Furthermore there are increasing reports of deaths in early adult life due to myocardial infarction in individuals who had Kawasaki disease in infancy. This raises the worrying possibility that coronary arteries damaged during Kawasaki disease may remain abnormal for many years and may predispose to coronary artery disease in early adult life. One worrying development has been the recognition in recent years that patients with the complete clinical picture may be only the tip of the iceberg, and that other children affected by the same process may present with only some of the diagnostic features. These patients who may have non-specific features such as fever and rash may still develop coronary artery aneurysms or die of the disorder. The recognition of this group of patients, and the diagnosis of their disorder, is obviously even more difficult than the diagnosis of classical Kawasaki disease.

Treatment

Fortunately the otherwise gloomy picture of a disease of unknown aetiology with dire consequences is brightened by the availability of treatment that may considerably reduce the risk of coronary artery disease. Initial studies undertaken in Japan showed that intravenous gammaglobulin infusions given in high dosage in the early phases of the disorder reduced the incidence of coronary artery aneurysms. Subsequent studies both from Japan and the USA have confirmed the beneficial effect of intravenous immunoglobulin, and this is now considered standard treatment for the disorder in many centres. Aspirin and perhaps other antiplatelet agents are widely believed to reduce the risk of coronary artery thrombosis, although there have been no controlled trials to confirm their efficacy. In patients who do develop myocardial thrombosis or severe myocardial ischaemia, treatment with antithrombotic agents, thrombolytic drugs and, in some cases, coronary artery surgery have been beneficial.

Implications

What are the implications of this information for paediatricians in the UK? Kawasaki disease is almost certainly grossly underdiagnosed in this country. While the incidence in the UK is 1.49 per 100,000 children, it is a lamentable epidemiological fact that a large proportion of cases of Kawasaki disease in the London area, up to 1984, were diagnosed by one paediatrician (the late William C Marshall). Failure to diagnose the disorder or distinguish it from other febrile exanthems of childhood may not have been of great importance while effective treatment was not available. However, in view of the reduction of coronary artery aneurysms by intravenous immunoglobulin and probably a reduction in mortality by aspirin and other antiplatelet agents, it is now of great importance that the disease be recognised early. While cases are most easily diagnosed in the second and third week when desquamation is occurring, this is probably too late to initiate treatment with immunoglobulin, which has been shown to be beneficial when given within the first 10 days of the illness. It is therefore important that the diagnosis be considered early. Physicians with experience of Kawasaki disease can usually recognise the disorder on its clinical features in the first 10 days of the illness. Suspected cases should therefore be discussed with, or referred to, a paediatrician with some experience of the disorder as soon as the possibility of the diagnosis is entertained. Investigations to exclude illnesses with similar manifestation, including staphylococcal and streptococcal disease, leptospirosis, and rickettsial disease should be promptly undertaken. Echocardiography to detect coronary artery dilatation or aneurysms should be undertaken as soon as possible, not only in children with the classical features of Kawasaki disease but also in infants with a prolonged febrile illness and two or three of the diagnostic features. Coronary artery abnormalities are easily visualised by experienced paediatric echocardiographers. However, cardiologists without considerable experience in paediatric echocardiography are unlikely to exclude reliably coronary artery disease in small children. As the finding of coronary artery aneurysms have both immediate and long term implications, patients in whom Kawasaki disease is seriously considered should be referred to a centre where the necessary echocardiographic expertise is available. As coronary artery aneurysms can develop as late as six weeks into the illness, patients with an initially normal echocardiographic study should have this repeated six weeks after the onset of the disorder.

There is a general consensus that aspirin should be started as soon as the diagnosis is considered. Recommended doses vary from 30–100 mg/kg/day in the acute stage reducing to an antiplatelet dose of 2 to 5 mg/kg/day once the fever has declined. Many centres prescribed dipyridamole in a dose of 5–10 mg/kg/day as an additional antiplatelet agent in patients who have detectable coronary artery aneurysms. Intravenous gammaglobulin in a dose of 400 mg/kg/day given daily for four days is of proved benefit in reducing the risk of coronary artery abnormalities.

A single dose of 2 g/kg given as a slow infusion over eight hours has recently been shown to be even more effective than the four dose regimen. Immunoglobulin treatment is expensive and not completely without risks, and there continues to be a debate as to whether it should be reserved for a subgroup of patients with the most severe disease. How this group should be identified remains an unanswered question. Several adverse prognostic features have been recognised including prolonged fever, severe anaemia, hypobulminemia, leucocytosis, and extreme thrombocytosis. None of these features is specific in identifying at risk patients and most authorities therefore currently advocate giving all patients with the disorder intravenous immunoglobulin.

In view of the long term risks of coronary artery thrombosis, patients with echocardiographically demonstrated abnormalities are usually treated with low dose aspirin for very prolonged periods of time, often for several years. Long term follow up of these patients is important. Finally, as with any relatively rare but serious disorder, elucidation of its aetiology, pathogenesis, and treatment is most likely to be achieved by widespread awareness of the disorder and by collaborative studies. Hopefully paediatricians in the UK will participate in further studies on this fascinating, but worrying paediatric disorder.

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1 Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involve-
5 Kato H, Koide S, Yokoyama M, Ito Y, Yano E. Coronary aneurysms in
Imaging in congenital deafness

One in every 1000 children has severe or profoundly severe hearing loss (greater than 50 dB hearing loss in the better hearing ear), which is detectable in the first year of life. In 90% the hearing loss is congenital and the causes are many and varied. A further one in 1000 has moderate to severe hearing loss and is not usually found until the age of 3 years.1 Diagnosis and recognition of congenital hearing loss at the earliest possible age is essential, as is recognition of the type and degree of deafness. Any part of the hearing organ may be affected. There is a wide range of abnormalities due to arrested or abnormal development, the aetiology and pathogenesis of which is completely or partially understood in only a few cases. Children with conductive deafness can be judiciously selected for surgical correction involving a minimum of risk to normal structures if the anatomical deformities are carefully outlined.

Radiology can play a significant part in the management of the child with congenital deafness. Evaluation of the bony structures in the ear can be made with accuracy. Structural deformities of inner and middle ears frequently coexist to give both a conductive and sensorineural component to the deafness. In the inner ear, radiological evaluation of congenital deafness must assess inner ear structure related to probable cochlear function and identify those structural abnormalities which carry the risk of cerebrospinal fluid fistula. In the middle ear radiology must assess the feasi-

bility of surgery for better sound conduction and the presence of any surgical hazards—for example, high jugular bulb, misplaced facial nerve, position of carotid artery—in addition to assessing structure and function in the favour-
able ear. Anatomical abnormality of the inner ear and middle ear are well recognised in association with the head and neck syndromes and at present imaging of the middle and inner ear is not routinely performed.

We suggest that patients should be selected for imaging in the following cases:

- In any syndrome known to be associated with structural deformity of the ear (see below).
- When there are certain spinal abnormalities present and including the Klippel-Feil syndrome.
- When there are abnormalities of the external ears including auricular appendages and pits.
- After attacks of meningitis and cerebrospinal fluid rhinorhoea.

We believe that high resolution fine section computed tomography in the neonatal period is essential and that evoked response audiometry and tomography are complementary procedures.2 Although screening tests would detect those infants with hearing impairment, imaging is the most important investigation particularly in those children for whom improvement is possible by surgical intervention.

Severe cochlear abnormalities are incompatible with