Parents worry about meningitis, but few have heard of Kawasaki disease, and most doctors have never seen a case. But Kawasaki disease is an important diagnosis not to miss in febrile children because treatment within the first 10 days of illness may prevent acute and long term coronary artery damage, which on rare occasions can be fatal. Diagnostic difficulty arises because many of the early clinical features of Kawasaki disease mimic other more common self limiting febrile illnesses. To make an early diagnosis of Kawasaki disease doctors should have a high index of suspicion in an irritable child with five or more days of fever, irrespective of other clinical features. This article aims to give an overview of Kawasaki disease for doctors who manage febrile children.

What is Kawasaki disease and who gets it?
Kawasaki disease is an acute febrile illness of early childhood, with about 80% of cases occurring between 6 months and 5 years. It is characterised by fever lasting at least five days and a constellation of clinical features that are used as diagnostic criteria (box 1). The clinical features are similar in all ethnic groups. Kawasaki disease is an acute inflammatory vasculitis of medium sized elastic arteries that has a striking propensity to damage the coronary arteries. As a consequence, it is the leading cause of acquired heart disease in children in developed countries.

Kawasaki disease was first reported in Japan more than 40 years ago, and the condition has since been described in most populations. It is not clear if Kawasaki disease is a new disease; reports of similar clinical features are rare in Japan before the mid-20th century, whereas in Europe infantile polyarteritis nodosa, a much rarer condition that shares many features with Kawasaki disease, has been described for more than a century.

How common is Kawasaki disease?
The incidence of Kawasaki disease varies worldwide, and it is up to 20 times more common in North East Asians than in white people. The highest rates are reported in nationwide surveys in Japan; in 2005-6 the annual incidence reached 184 per 100 000 children under 5 years. Epidemiological studies report an incidence of up to 95 per 100 000 in Korea, and 104 per 100 000 in Taiwan in children under 5. In comparison, an analysis of hospital episode statistics in England reported an incidence that has increased over the past two decades to eight per 100 000. The higher incidence in North East Asians persists after migration to countries with low incidence. Parents of Japanese children with Kawasaki disease are more likely to have had the condition as children, and the risk in siblings of children with Kawasaki disease is also significantly higher. Reports of cases in rapidly developing countries such as India have recently increased, perhaps because of improved recognition or the appearance of Kawasaki disease at a time of rapid industrialisation.

What causes Kawasaki disease?
Despite four decades of research, attempts to identify a causative pathogen or environmental trigger have so far been unsuccessful (see box on bmj.com). Epidemiological data suggest that one or more widely distributed infectious agent triggers an abnormal inflammatory response in a genetically predisposed child. An infectious trigger is supported by the pronounced seasonality, with winter and spring peaks in most temperate countries and summer peaks in many Asian countries, together with reported epidemics of the disease. The clinical features can initially be mistaken for severe infection.

Sources and selection criteria
We searched PubMed and Cochrane databases using the keywords “Kawasaki disease” or “mucocutaneous lymph node syndrome”. We reviewed abstracts from the last three international Kawasaki disease symposiums (2001, 2005, 2008). Our focus was on systematic reviews, national guidelines, and randomised controlled trials. We reviewed the reference lists of all articles retrieved together with those in our personal reference libraries. For the treatment section we looked at systematic reviews and randomised controlled trials only.
Kawasaki disease is relatively rare in the first few months of life, which suggests that most adults have been exposed to the causative agent and that protective transplacental antibodies protect the newborn infant. Supportive data are rare, however, because the infectious trigger(s) are unknown. Kawasaki disease is much less common in older children and adults and recurs in only a minority of children. We suggest that most children probably encounter the causative pathogen(s) in early childhood—possibly asymptomatically—and develop protective immunity.

The role of bacterial superantigens in Kawasaki disease remains controversial. Like other inflammatory diseases—such as rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis—Kawasaki disease is genetically complex, with many genes contributing modest effects to the overall risk, and no single gene “causing” the disease.

**How is Kawasaki disease diagnosed?**

Children with Kawasaki disease are febrile and extremely irritable, much more so than children with other febrile illnesses (fig 1). No diagnostic test is available. Clear diagnostic criteria have been established by the Japanese Ministry of Health research committee and have been adopted by the American Heart Association and American Academy of Pediatrics (box 1).

The clinical features usually appear sequentially, and a diagnosis of Kawasaki disease should be reconsidered regularly in a young child with persistent fever. The differential diagnosis of Kawasaki disease is potentially wide, but it is most often confused with streptococcal and staphylococcal infections (including scarlet fever and toxic shock syndrome), viral infections such as measles and glandular fever, or drug reactions such as Stevens-Johnson syndrome. Children tend to be listless and easily fatigued for four to six weeks after the acute illness, which usually lasts one to two weeks without treatment. It is in the subacute phase that coronary artery aneurysms may progress. Box 2 summarises the laboratory features of Kawasaki disease.

**Box 1 Clinical diagnostic criteria**

Fever of at least five days’ duration and at least four of the following five clinical features:

- Polymorphous exanthema (but not petechial, bullous, or vesicular lesions)
- Bilateral non-exudative conjunctival injection
- Changes in lips and oral cavity (but not discrete oral lesions or exudates)
- Changes in the extremities, including erythema or indurative oedema, and later (in the second week of illness) membranous desquamation starting around the nail bed
- Cervical lymphadenopathy, often unilateral and large (≥1.5 cm)
The nature of the rash in Kawasaki disease is variable. It may be made up of pink maculopapular lesions (morbilliform rash) (fig 2), sharply demarcated red lesions (erythema multiforme), or generalised or uniform redness (scarlatiniform rash). Petechial, vesicular, or bullous lesions are not a feature and suggest an alternative diagnosis. The rash often begins in the nappy area and spreads to the rest of the torso, extremities, and face. This nappy rash may peel during the acute illness.

A unique feature of Kawasaki disease is acute inflammation at the site of a previous BCG inoculation. The hands and feet may be swollen, erythematous, and painful to touch or on weight bearing, and the child often refuses to walk or crawl. In older children, desquamation of fingers and toes (fig 3), which occurs after the acute illness and is therefore not helpful diagnostically, may be the only peripheral feature. Conjunctival injection, which appears early in the illness, is not associated with purulent discharge and often spares the limbus, an avascular zone around the iris. Oropharyngeal changes may affect the lips, tongue, or pharynx, but pharyngeal exudates and ulcers are not seen. Cervical lymphadenopathy, the least frequent diagnostic feature, is more common in older children. A solitary lymph node is often non-fluctuant, firm, and mildly tender.

Rarely, there is severe peripheral vasculitis, with Raynaud’s phenomenon. Severe vasculitis and vasospasm can cause distal ischaemia and result in gangrene of the fingers and toes.12

Incomplete Kawasaki disease

The 15-20% of children with Kawasaki disease who have fever and fewer than four principal features may still develop coronary artery dilatation or aneurysms. They are classified as having incomplete Kawasaki disease, a particularly challenging diagnosis that is more common in infants under 6 months.15

The American Heart Association and American Academy of Pediatrics have published an algorithm to help in the early detection of incomplete Kawasaki disease (see bmj.com).13 This algorithm represents expert consensus and uses commonly available laboratory tests and echocardiography, when indicated. It has been evaluated retrospectively but not yet prospectively in the clinical setting.13
How is Kawasaki disease treated?

Intravenous immunoglobulin

Randomised controlled trials have shown that a single infusion of 2 g/kg of intravenous immunoglobulin given 5-10 days after the onset of fever eliminates fever in 85-90% of children within 36 hours and significantly reduces the risk of coronary artery aneurysms. A single intravenous immunoglobulin infusion of 2 g/kg produces a better outcome than 400 mg/kg/day for five days. The benefit of starting immunoglobulin before the fifth day of illness is uncertain, but treatment should be given beyond day 10 if fever or inflammation is ongoing. Guidelines recommend a further dose of 2 g/kg in children who remain febrile 36 hours after the first dose of immunoglobulin.

Aspirin

A Cochrane review and a meta-analysis of treatment with aspirin highlighted a lack of trial evidence, although aspirin has been standard treatment for Kawasaki disease since its initial description in Japan because of its anti-inflammatory and antiplatelet activities. The American Academy of Pediatrics acknowledges that practice varies with respect to dose and duration of treatment, with most clinicians prescribing 80 mg/kg/day until the child is afebrile and 3-5 mg/kg/day thereafter until a normal echocardiogram is seen at six weeks after the onset of symptoms. In Japan, however, it is common practice to give aspirin 30 mg/kg/day throughout the acute and subacute phases. Persistent coronary artery abnormalities require specialist management.

Corticosteroids

In contrast to other systemic vasculitides, which usually respond to steroids, evidence that corticosteroids reduce coronary artery abnormalities is inconclusive. A meta-analysis of trials of variable quality concluded that the addition of corticosteroids was beneficial. However, a recent well conducted, multicentre, double blinded, placebo controlled randomised trial reported no difference in coronary artery changes, days spent in hospital, and length of fever for children receiving standard treatment of intravenous...
immunoglobulin and aspirin plus 30 mg/kg of methyl-prednisolone compared with standard treatment plus placebo. Although trial evidence is lacking, 30 mg/kg methylprednisolone daily for up to three days is usually recommended if there is no response to the second intravenous immunoglobulin infusion.

Other interventions
Controlled trial data are not available for other interventions such as plasma exchange, agents that block platelet receptors and tumour necrosis factor, pentoxifylline, cyclophosphamide, and statins. Live vaccines—including measles, mumps, and rubella—should be delayed after treatment with intravenous immunoglobulin, because neutralising antibodies may decrease vaccine immunogenicity. The recommended interval between intravenous immunoglobulin and live vaccines varies—three months in the United Kingdom and 11 months in the United States, Canada, and Australia.

What are the cardiovascular complications of Kawasaki disease?
Clinical signs
Cardiovascular examination during acute Kawasaki disease may show tachycardia greater than expected for the patient’s age and fever. Rarely, pancarditis and heart failure can occur, with muffled heart tones and gallop rhythm suggestive of either myocarditis or pericardial effusion. Myocarditis is thought to be common, but it rarely results in clinically relevant depression of myocardial function.

Coronary artery pathology
Consensus guidelines from the American Heart Association on the diagnosis, treatment, and long term management of Kawasaki disease state that mild diffuse dilatation of coronary arteries occurs in 30–50% of cases and starts on average 10 days from onset of fever. In most cases, this dilatation is transient and regresses within six to eight weeks of fever onset. However, 20% of coronary artery lesions progress to true aneurysms, although this is reduced to about 5% with intravenous immunoglobulin treatment. In about 1% of cases, aneurysms become “giant aneurysms” (>8 mm diameter) (fig 4), which carry a poor prognosis; they may heal with stenosis and cause distal myocardial ischaemia, or more rarely they may rupture.

Although Kawasaki disease preferentially affects coronary arteries, other medium to large arteries may be affected. Proximal brachial arteries, femoral arteries, iliac arteries, and extraparenchymal renal arteries most often show aneurysmal changes. The aorta may show aneurysmal dilatation in postmortem specimens.

An unclear vasculitic process within the coronary arteries increases endothelial activation and renders the endothelium procoagulant. In addition, the blood becomes hypercoagulable because of an increased number of activated platelets. In the presence of large aneurysms, stagnation of flow and local changes in shear stress further promote thrombosis. A large case series of Japanese children who had myocardial infarction showed that infarction as a result of occlusive thrombosis in the coronary arteries is most common during the first 6–12 months after onset. The standardised mortality ratio during the convalescent stage of Kawasaki disease for Japanese children with cardiac sequelae has been reported to be as high as 2.55 in boys. The in-hospital mortality rate is 0.17% in the US. Cardiac arrhythmias are more common after
SUMMARY POINTS

- Kawasaki disease is an acute febrile illness that mainly affects children under 5.
- It is the most common cause of acquired heart disease in children in the developed world.
- Diagnosis is based on fever of at least five days' duration and four of five diagnostic clinical criteria.
- The typical clinical features appear sequentially and are rarely all there at presentation.
- The diagnosis should be considered in any child with prolonged fever, irrespective of other features.
- Intravenous immunoglobulin and aspirin given 5-10 days after onset of fever reduce the incidence of coronary artery lesions from around 20% to around 5%.

Kawasaki disease and may occur independently of coronary artery involvement. Heart block and fever may occasionally be the only presenting features of Kawasaki disease.

What are the longer term implications of Kawasaki disease?

The original Japanese cohorts are now approaching middle age and are still too young for modest effects on the risk of clinically important atherosclerosis to be detected. In those with obvious changes to the coronary arteries during acute Kawasaki disease, surrogate markers of atherosclerosis are abnormal in many studies, which suggests that later cardiovascular risk may be increased.

About half of patients who recover from Kawasaki disease have serum lipid abnormalities, mostly abnormally low high density lipoprotein, but some have raised low density lipoprotein or triglycerides.

Patients with giant aneurysms who survive may still develop ischaemic heart disease years later because of de novo development of localised coronary stenosis.

Children with giant coronary artery aneurysms have a high probability of myocardial infarction or ischaemic events.

The risk of future cardiac events for children with small aneurysms or transient coronary dilatation (lasting only for 6-8 weeks) is uncertain. The American Heart Association has produced cardiovascular risk stratification guidelines for children with Kawasaki disease (see bmj.com).

Conclusion

Kawasaki disease is an important cause of fever in young children. It results in a high incidence of cardiovascular damage if not treated promptly. The diagnosis should always be considered in the young child with an unexplained and persistent fever, despite the absence of full diagnostic criteria.