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PRACTICE

EASILY MISSED?

Kawasaki disease

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at practice@bmj.com.

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Case scenario

A 2 year old boy was brought to see the general practitioner by his parents because of a four day history of fever. His parents noticed a rash and slightly "bloodshot" eyes the day before. The GP diagnosed a viral illness, offered reassurance, but gave good safety netting advice. The boy re-presented to his GP three days later, still intermittently febrile, irritable, and with an angry looking widespread morbilliform rash and a sore mouth. Kawasaki disease was suspected, and he was admitted to hospital where he received prompt treatment with intravenous immunoglobulin and high dose aspirin. An echocardiogram, performed during admission was normal, as were those during follow-up.

What is Kawasaki disease?

Kawasaki disease is an acute inflammatory vasculitis of medium size arteries that occurs mainly in children aged 6 months to 5 years but can occur at any age, including younger infants, and even occasionally in adults.[1-3] Although one or multiple infectious triggers are most likely, the precise cause is unclear. Kawasaki disease is the commonest cause of acquired heart disease in children in industrialised countries because the coronary arteries are affected in about a quarter of untreated cases. The incidence of acquired heart disease in children is rising.[4]

Why is Kawasaki disease missed?

A recent observational study of Kawasaki disease set in primary care reported a delay of more than 10 days (range of the time for the total sample between GP presentation and admission was 0-86 days) between first presentation and hospital admission for 7% of children.[11] In the initial stages the fever and rash of Kawasaki disease can mimic viral exanthemata, such as parvovirus, adenovirus, and measles, as well as group A streptococcal infection. Parents might be falsely reassured that their child has a simple febrile illness and delay seeking further advice when symptoms persist or new symptoms appear. In any infant under 6 months, a prolonged fever of seven days or more, with laboratory evidence of inflammation, should be considered as Kawasaki disease and be referred for assessment and possible treatment.[12]

Why does it matter?

Kawasaki disease can cause damage and dilation of the coronary arteries, including aneurysms. These may be small, but in some, there can be substantial dilation or even giant aneurysms (>8 mm internal diameter). These can thrombose acutely or can heal with stenosis, causing myocardial ischaemia many months or years later.[13] In addition, there might be acute myocarditis, leading to poor heart function, valvular regurgitation, or pericardial effusion.

It is important that Kawasaki disease is diagnosed early because treatment with intravenous immunoglobulin within five to 10 days of fever onset reduces the incidence of coronary artery lesions from 25% to ~5%.[12 13] Delays in treatment might lead to unnecessary morbidity and occasionally death. The mortality rate is about 0.2% and is most commonly secondary to thrombosis of giant aneurysms or later myocardial ischaemia and infarction.[12] Infants under 6 months, who have had fever for seven days or more, are often diagnosed late owing to

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How common is Kawasaki disease?

England—8.39 per 100 000 children under 5 years[5]

Australia—9.34 per 100 000 children under 5 years[6]

Japan—239 per 100 000 children under 5 years[7]

Korea—134 per 100 000 children under 5 years[8]

Taiwan—66 per 100 000 children under 5 years[9]

Hawaii—210 per 100 000 Japanese American children under 5 years, and 13 per 100 000 white children under 5 years[10]

incomplete features, and they might have serious, potentially life--threatening complications.[14]

How is Kawasaki disease diagnosed?

Clinical features

The diagnosis of Kawasaki disease is made on clinical grounds. Fever is universal and typically unresponsive to antipyretics and antibiotics. The diagnostic clinical criteria are individually insensitive and non-specific. Definite Kawasaki disease is characterised by prolonged fever (usually defined as ≥5 days) and at least four out of five key diagnostic features (box). Children with prolonged fever and suspected Kawasaki disease should be referred promptly for further assessment.

The clinical features often occur sequentially and some might have resolved by presentation, so a focused history is essential. Children who have been vaccinated with BCG might have inflammation at the vaccination site. Children with Kawasaki disease are often noticeably irritable. Incomplete Kawasaki disease (fever but less than four diagnostic criteria) is common (15-20% of all cases), so a high index of suspicion is needed for any young child or infant with prolonged fever and no clear diagnosis. Incomplete Kawasaki disease is associated with increased incidence of coronary artery abnormalities, possibly caused by delayed diagnosis.[12 14]

Investigations

No diagnostic test is available for Kawasaki disease. Laboratory features can aid the diagnosis but, as with the clinical diagnostic criteria, they lack individual specificity and sensitivity. Leucocytosis and neutrophilia are usually found. Thrombocytosis is common but occurs subacutely (week two to three), so it is not helpful diagnostically. Inflammatory markers are typically raised and mild abnormalities of liver function tests are common. White blood cells are often present in the (sterile) urine or cerebrospinal fluid, or both. A microbiologically confirmed infection is also present in a third of patients with Kawasaki disease and should not preclude the diagnosis.[15]

A transthoracic echocardiogram is essential to identify coronary artery abnormalities, assess myocardial and valvular function, and exclude a clinically important pericardial effusion. These changes might be identified at presentation in severe cases but usually develop in the subacute phase (2-3 weeks). Echocardiography is therefore not useful diagnostically, and a normal study should not influence the decision to treat Kawasaki disease. Echocardiography is performed at presentation, with follow-up echocardiograms at two weeks—if there is concern—six weeks, and often at six months. Subjective brightness of the walls of the coronary arteries, mild dilation (ectasia), or frank aneurysms might be seen.[16]

How is Kawasaki disease managed?

Hospital admission is necessary. On the basis of randomised control trials, intravenous polyclonal immunoglobulin has become the established treatment, and it reduces the risk of coronary artery aneurysms from 25% to less than 5%.[12 17] Aspirin is given, although dosing regimens vary.[17 18] Additional corticosteroids have been recommended in some countries for severe and evolving cases.[17] About 15% of patients do not respond to immunoglobulin, and subsequent treatment often comprises a second infusion of immunoglobulin and intravenous methylprednisolone.[12 17 19]

Most children in industrialised countries have few long term sequelae if treated promptly and appropriately. A small proportion of children with major coronary artery damage will require ongoing specialist management. Some patients report behavioural changes and desquamation of fingers and toes with subsequent febrile illness.[20] Live vaccines (such as measles, mumps, and rubella) should be delayed for 11 months after treatment with intravenous immunoglobulin. Recurrence is rare (<1%), the risk in siblings is probably modestly increased (about 10 times the population risk in Japan).[12] Kawasaki disease is not contagious. Families of children with this disease might benefit from follow-up with a doctor familiar with the condition to allay anxiety and answer specific queries, even if there are no long term coronary artery abnormalities.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: DB has salary and support for research into Kawasaki disease from the National Health and Medical Research Council, and Murdoch Childrens Research Institute; he also has invitations (partly reimbursed) to present Kawasaki disease-related research findings at conferences of the European Society for Paediatric Infectious Diseases, World Society for Paediatric Infectious Diseases, International Kawasaki Disease Symposia, and the World Congress of Cardiology; DB is also involved in the preparation of educational material for the Kawasaki Disease Foundation, Australia. None of these agencies or bodies had any input or influence over the manuscript at any stage. AH and RT have no interests to declare.

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The diagnostic features of Kawasaki disease[12]

Fever (>39˚C) for at least four days and at least four of the following features, after exclusion of other similar diseases*

- Bilateral non-exudative bulbar conjunctival injection
- Polymorphous exanthema
- Changes in the extremities (acute—erythema of palms and soles, oedema of hands and feet. Subacute—periungual peeling of fingers and toes)
- Changes to lips and oral cavity (red, fissured lips, strawberry tongue, erythema of oropharyngeal mucosa, without exudates)
- Cervical lymphadenopathy (≥1.5 cm, usually unilateral, rare in infants)

Key points

- Consider a diagnosis of Kawasaki disease in young children with irritability and prolonged fever (>5 days) and refer to hospital for assessment and treatment
- Incomplete Kawasaki disease—fever but fewer than four of the other diagnostic criteria (bilateral conjuntival injection, polymorphous exanthema, changes to the extremities or lips and oral cavity or both)—represents 15-20% of cases
- Treatment with intravenous immunoglobulin within five to 10 days of fever onset reduces the incidence of coronary artery lesions from 25% to ~5%
- A transthoracic echocardiogram is essential to identify coronary artery abnormalities, assess myocardial and valvular function, and exclude clinically important pericardial effusion, but a normal study does not exclude Kawasaki disease

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