# Kawasaki Disease - A Review

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*INTRODUCTION*

*Kawasaki disease (KD) was first described in 1967 by Tamsiku Kawasaki and remains the subject of extensive medical research to the present day. It has a worldwide distribution and is now recognised as a relatively common disorder even in the Western world. KD is of particular interest as it causes significant morbidity and mortality in the paediatric age group and has become the commonest cause of acquired heart disease in children. Despite exhaustive research, the cause of KD remains unknown.*

## *EPIDEMIOLOGY*

The epidemiology of KD suggests an infectious aetiology in that there has been documented clustering of cases, epidemics at approximately 3 year intervals, and strong clinical similarities with toxic shock syndrome and scarlet fever. Moreover, in Japan it has spread in waves from one region to the next. The disease occurs almost exclusively in young children, with 80% of cases being less than 4 years of age. The peak incidence occurs in the 9 to 11 month olds and KD is very rare after 8 years of age. The estimated incidence in the UK is 1.49 per 100 000 children. No association has been found between KD and HLA types in children.

## *CLINICAL FEATURES*

The diagnosis of KD is a clinical one but requires the exclusion of a number of other disease processes, most of which are infectious in origin, with the help of laboratory investigations. The current diagnostic criteria of KD are shown in Table 1.

Many children with KD may have atypical presentations and therefore may not fulfil the classical criteria for the diagnosis to be made confidently.

*Fever* is the main clinical feature and is usually high spiking, remittent and prolonged for 5 to 14 days. Then low grade fever may follow for 14 to 21 days. The child is usually very irritable and miserable especially in the first weeks of the illness. Typically there is bilateral bulbar *conjunctival injection* without any exudate. The *lips* are reddened, dry, fissured and bleed readily. There is also an accompanying *oropharyngitis* and a *strawberry tongue*. Although there is intense inflammation mucosal ulceration is *not* a usual feature of the disease. The *palms* and *soles* typically become erythematous, oedematious and indurated followed by *desquamation* of the skin of the fingers and toes about 10 to 20 days after the onset of the fever. The skin *rash* is polymorphous and may appear urticarial, scarlatinform, morbilliform or similar to the target lesions of erythema multiforme and is distributed predominantly on the trunk, extremities and perineum. Vesicles and bullae are not a feature of KD. About 50 to 70% of cases have tender cervical *lymphadenopathy* with at least one lymph node larger than 1.5cm in diameter. *Arthralgia* and *arthritis* of the knees, ankles and wrists occur in up to 30% of cases and may persist for weeks and sometimes for as long as three months. *Aseptic meningitis* is a feature in about 25% of cases. Cardiovascular involvement is the most feared complication of the disease and occurs in about 25-30% of cases. *Myocarditis, pericarditis,* and *valvular regurgitation* are recognised features of KD and ECG changes are present in up to 33% of cases. *Coronary arteritis* occurs in the first 2 weeks of the illness and this may lead to coronary artery *aneurysms* within 4 weeks of onset.

Other features of KD include mild *hepatitis, hydrops of the gall bladder, diarrhoea, pneumonitis,* and a sterile *otitis media*. Diagnosis of KD must be considered in all cases of unexplained and prolonged fever even if only 2 or 3 features are present.

## *DIFFERENTIAL DIAGNOSIS* (Table 2)

Other childhood infections with similar presentation include streptococcal scarlet fever, toxic shock syndrome, measles, rubella, leptospirosis, infections caused by enterovirus, parvovirus and rickettsiae.

## *PATHOGENESIS*

The major pathological feature of KD is a vasculitis of the small and medium sized arteries

throughout the body. Microscopy shows endothelial cell death, leucocyte infiltration in the muscular and adventitious layers of the vessels leading to structural disruption and aneurysm formation. Secondary thrombosis may occur at the site of the aneurysms. A severe pancarditis may lead to necrosis of the myocardium early on in the course of the illness. This complication must be distinguished from the myocardial ischaemic necrosis that occurs secondary to coronary artery thrombosis at a later stage of the disease. Healing of the injured vessels leads to extensive deposition of collagen which may become sites for early atheromatous lesions. The vascular damage is caused by activation of the inflammatory cascade against endothelial cells in particular. The triggering factor remains unknown although a class of toxins called superantigens which are produced by various pathogenic organisms are thought to be linked to the disease.

***TREATMENT RECOMMENDATIONS*** (Table 3)

The aim of treatment is to reduce the inflammatory response in the myocardium and coronary artery wall. High dose *intravenous immunoglobulin (IVIG)* at a dose of 2 grams per kilogram body weight given over 10-12 hours to achieve high serum levels reduces significantly the risk of coronary aneurysms and should be given as early as possible into the course of the disease.

*Aspirin* at 30mg/kg/day during the acute phase and reduced to 2-5mg/kg/day as soon as the fever subsides and continued for 6-12 weeks is commonly prescribed. For established cases of coronary aneurysms some centres give low-dose aspirin for life in addition to *dipyridamole* 5-10mg/kg/day. Despite the wide use of aspirin and other antiplatelet drugs in KD there

***Table 1: Diagnostic Criteria for Kawasaki Disease***

1. Fever for 5 or more days

2. Presence of any 4 of the following criteria:

- Bilateral conjunctival injection
- Changes in mucosae of the upper respiratory tract e.g. pharyngitis, dry cracked lips, strawberry tongue.
- Changes in peripheries e.g. oedema, erythema, desquamation
- Polymorphous rash
- Cervical lymphadenopathy

3. Exclusive of: Staphylococcal & streptococcal infections, measles, rubella, rickettsial infections, Stevens - Johnson syndrome, drug reaction & juvenile chronic arthritis.

*N.B. in the presence of coronary artery aneurysms, fever plus three of the five criteria in (2) is sufficient.*

***Table 2: Differential Diagnostic of Kawasaki Disease***

- Streptococcal Scarlet Fever
- Staphylococcal Toxic Shock Syndrome
- Viral infections: measles, rubella, parvovirus, enterovirus
- Other agents: Rickettsiae, Leptospira
- Stevens - Johnson Syndrome

***Table 3: Treatment of Kawasaki Disease***

***"Conventional" Treatment:***
- Intravenous Immunoglobulin (IVIG): 2 g/kg i.v. over 10-12 hours
- Aspirin: high dose: 30 mg/kg/day; low dose: 2-5 mg/kg/day

***"Experimental" Treatment:***
- Anticoagulation
- Thrombolytic agents
- Coronary Artery Surgery

***Table 4: Important Managment Points of Kawasaki Disease***

- Diagnosis is made on clinical grounds.
- Early diagnosis & treatment (in the first 10 days) is vital to achieve maximum benefit
- Suspected cases should be referred EARLY for admission to hospital
- The diagnosis of KD should be considered in any young child, especially an infant, with unexplained fever lasting more than 5 days
- Long-term follow-up, sometimes lifelong, is recommended.

have been no controlled trials of their efficacy to date.

The role of corticosteroids is still unclear and at the present time they are not recommended even if the reason for this is largely based on a study which was flawed with selection bias of its patients. In children with myocardial ischaemia or infarction, anticoagulation, thrombolytic therapy and coronary artery surgery have all been tried on an individual basis.

### *PROGNOSIS*

In the acute phase of the illness aneurysms are detected in 20-40% of cases. The mortality in the acute and early convalescent phase is about 1%. Fortunately, most aneurysms regress in the first 2 years after the illness but there is a small risk (5%) of late stenosis developing at the site of previous aneurysms. Asymptomatic myocardial infarction and chronic myocardial ischaemia are a recognised complication of KD. Histological abnormalities of the coronary arteries may persist for many years after initial presentation and there have been case reports of related deaths in early adult life. The actual risk of myocardial infarction later in life after coronary artery involvement is unknown but all cases will need lifelong surveillance. Adverse prognostic factors include a prolonged fever, severe anaemia, hypoalbuminaemia, leucocytosis and thrombocytosis.

### *DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS*

Diagnosis is easiest in the second or third week of the illness but by then the benefit of medical treatment is largely lost. Therefore, it is essential for the diagnosis to be made in the first 10 days from onset. This necessitates a high index of suspicion and early referral to hospital for in-patient care. An echocardiographic assessment should be carried out as soon as possible after diagnosis. If this is normal then a second one after 6 weeks is mandatory. If the initial echocardiogram is abnormal then weekly examinations are carried out. The diagnosis of KD must be considered in any young child with an unexplained fever for more than 5 days even if all the diagnostic criteria are absent. Finally, the prognostic implications and the need for long-term medical surveillance must be clearly explained to the parents.

*Table 5: Factors Predicting Coronary Artery Involvement*

- Age below 12 months
- Fever for more than 16 days
- Recurrent fever after an afebrile 48 hour period
- Cardiac arrhythmias
- Cardiomegaly
- Caucasian
- Anaemia
- Hypoalbuminaemia
- Severe thrombocytosis (> 2000 x $10^6$/ L)
- Severe leucocytosis

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