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Learning Objectives

1. To learn about the epidemiology, aetiopathogenesis, clinical features and differential diagnosis of Kawasaki disease (KD)
2. To learn about the acute and long-term management of KD

Case Report

A 2-year-old boy presented with high-grade fever for 8 days. The baby had been irritable and fretful and was refusing feeds. The mother consulted a paediatrician who prescribed amoxicillin. The fever, however, persisted and the baby developed swelling over the dorsum of hands and feet. The mother also noticed a rash over the trunk along with red lips and red tongue. Both eyes were con-

gested and there was a swelling on the left side of the neck. As the fever was continuing, she sought consultation from another paediatrician who opined that the baby needed hospitalization for further workup.

He ordered an infection workup, obtained blood and urine cultures and started intravenous ceftriaxone. The baby continued to run fever.

Investigations showed a neutrophilic leucocytosis, raised C-reactive protein levels and an elevated erythrocyte sedimentation rate. Blood and urine cultures were sterile.

At this time a clinical review suggested a possibility of this being Kawasaki disease. 2D echocardiography did not reveal any coronary artery abnormality.

The parents were counselled and a decision was taken to administer intravenous immunoglobulin (IVIg) 2 g/kg along with aspirin 30 mg/kg/day. The baby showed prompt clinical improvement. The irritability disappeared within a few hours and the fever was passive by the next day. The mother noticed that the skin over fingers and toes had started to peel. A repeat haemogram at this time showed thrombocytosis. The dose of aspirin was reduced to 3 mg/kg/day and the baby was discharged with a follow-up appointment after 2 weeks.

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Introduction

Kawasaki disease (KD) is an acute, self-limiting, childhood medium-vessel vasculitis. Initially described in 1967 by Dr. Tomisaku Kawasaki in Japanese children as an acute mucocutaneous lymph node syndrome [1–3], KD may lead to coronary artery abnormalities (CAAs) in up to 25% of patients if left untreated. It is for this reason that KD is considered a medical emergency.

Epidemiology

KD is the most common cause of an acquired heart disease in children in developed countries. It is now often considered to be the most common vasculitic disorder in children. The three highest incidence figures of KD in the world come from the Far East, viz., Japan, Korea and Taiwan. In these countries, not only is the incidence very high, it is continuing to show a rise on a year-to-year basis [4–10].

Nationwide surveys conducted in Japan since 1970 show that there have been three epidemics of KD in Japan and also that the incidence of KD has increased by more than two times in the last two decades [6–9]. Japan reports the highest incidence of KD in the world – the present figure being 265/100,000 children below the age of 5 years. Korea has the second highest incidence at 134.4/100,000 children below five. In Taiwan the current incidence is 82.8 per 100,000 [3]. Based on statistical projections, it is estimated that by 2030, there will be 1 in 700 people living in Taiwan with a history of KD. The corresponding figure for the USA is 1 in 1600 [4–6].

The incidence of KD, however, has remained static in Europe as well as North America. In India, anecdotal reports suggest that the recognition of KD has increased significantly over the last two decades, but confirmatory epidemiologic data on incidence are not available. A hospital-based study from Chandigarh showed that the incidence was 4.54/100,000 children below 15 years, but this figure is, in all likelihood, a gross underestimate [11]. There is no doubt, however, that over the years awareness of KD

amongst paediatricians in India has increased significantly. In the years to come, KD may soon replace rheumatic fever to become the leading cause of acquired heart disease in children in India, just as in Japan, Europe and North America.

KD affects the young with 85% of cases being below 5 years. Although it is uncommon in children below 3 months, KD has been reported in neonates as well. In India, however, the median age of occurrence of KD is higher than in Japan probably because KD in infancy and young children is being missed in our country. Boys seem to be affected more commonly than girls. The male/female ratio at Chandigarh has been 1.8:1 [2, 3, 11–13].

Fascinating data on seasonal variations in the incidence of KD have emerged, and these have linked the incidence figures of KD in some countries (especially Japan and the USA) to tropospheric wind patterns emerging from Central Asia. Such associations have, however, not been proven in other countries, as, for instance, Canada [14].

Aetiology

The causation of KD still remains an enigma. There have been various hypotheses and postulates regarding its aetiology [15, 16].

Infectious: There are multiple factors which suggest that KD could be an infectious illness. Occurrence of the disease in childhood and its virtual absence in adulthood suggest that it may be an infectious disease, and exposure in childhood confers protective immunity, thereby protecting the individuals in adulthood. Rarity of its occurrence in early infancy suggests that maternal antibodies may have a protective effect. In addition, clustering of cases in some seasons, few reports suggesting occurrence in families or communities and the clinical presentation with fever, rash and lymphadenopathy, also suggests that it might be an infectious illness. However, till date, no infectious agent has been incriminated with certainty. Although several micro-organisms (e.g. *Streptococcus*, *Staphylococcus*, *Epstein-Barr virus*, *Parvovirus*, *Coronavirus*) have been linked with KD, infection alone cannot explain the pathogenesis of the disease.

Superantigen mediated: The presence of excess of T-lymphocytes with $V\beta_2$ in the coronaries, intestinal mucosa and blood in children with KD suggests that the disease might be superantigen mediated. Also, some of the clinical features of KD mimic those of toxic shock syndrome which is a superantigen-mediated disorder.

Environmental: Researchers have also suggested that there might be an environmental trigger which causes this illness. Seasonal and geographical clustering can be explained on this basis.

Genetic: Recent evidence based on genome-wide association studies suggests that a genetic basis of KD seems entirely plausible. Evidence for this hypothesis comes from several epidemiologic data which show that children of certain genetic background seem to have a much higher predisposition to KD. For instance, the incidence of KD amongst children of Japanese ancestry in Hawaii is much higher than that in other races residing there. In fact, the incidence of KD in children of Japanese ancestry there is almost similar to the incidence in Japanese children residing in Japan.

However, till date, no single gene has been implicated, and there is no suggestion of it being an inherited disorder. Onouchi et al. have shown the association between KD and ITPKC functional polymorphisms [15, 16]. It appears that KD is triggered in genetically predisposed children on exposure to some infectious or environmental agent.

Pathology

KD is a systemic medium-vessel vasculitic disorder with a striking predilection for the coronary arteries. This preferential involvement of the coronary arteries is unique to this condition. The inflammation involves primarily the intima and media leading to damage of the internal and external elastic lamina. The affected vessel may subsequently become ectatic or may show aneurysmal dilatation. Healing of these vessels may, in due course, result in stenosis and coronary thrombosis. Large coronary aneurysms, and especially giant aneurysms, may never regain normal anatomy [2, 3].

The clinical correlates of these changes should be borne in mind. On echocardiography, a coronary artery that gets dilated in the acute phase may regain its normal diameter during convalescence. However, intravascular ultrasound studies have shown that the vessel wall may never regain its recoil and elasticity even when echocardiography suggests a normal anatomy. Coronary artery involvement can also be studied by doing computerized tomography (CT) angiographic studies (Fig. 35.1).

Coronary vessels affected in KD have a predisposition to develop calcification during the healing phase. This calcification may render the affected vessels unsuitable for procedures such as angioplasty and stent placement later in life.

KD can also affect other arteries like the femoral and axillary. These would, however, get involved only if there has been coronary artery



Fig. 35.1 CT angiogram of a child with Kawasaki disease showing multiple aneurysms (arrows) in left anterior descending (LAD) branch of left main coronary artery

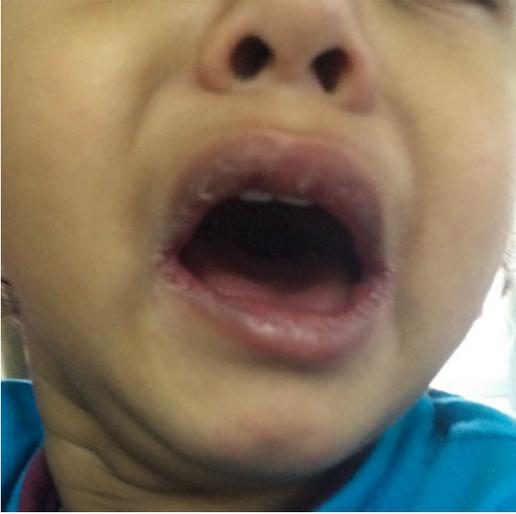


Fig. 35.2 Redness of lips

involvement. It is unusual to have a visceral artery involvement in KD.

Clinical Features

Diagnosis of KD is based on recognition of a constellation of clinical findings which appear in a temporal sequence (Figs. 35.2 and 35.3) [13, 17].

Clinical Features of Kawasaki Disease

Fever >5 days plus at least four of the following:

- Bilateral conjunctival injection
- Changes in oropharyngeal mucous membranes
- Changes in peripheral extremities
- Polymorphous rash
- Cervical lymphadenopathy

Illness not explained by any other disease condition

1. *Fever*: This is often high grade, may exceed 40 °C and lasts for more than 5 days. The fever typically does not respond to antimicrobials and is associated with irritability which may at times be extreme.



Fig. 35.3 Skin peeling

2. *Conjunctival injection*: Non-purulent, bilateral conjunctival injection sparing the limbus is seen in about 93% of children with KD. Watering from the eyes is unusual in KD and its presence should point towards an alternate diagnosis.
3. *Changes in lips and the oral mucosa*: The presence of redness, swelling and cracking of lips with strawberry tongue are strong pointers towards the diagnosis. The presence of follicular tonsillitis points against the diagnosis of KD.
4. *Changes in extremities*: Erythema and oedema of the dorsum of hands and feet are seen in KD. Indurated erythema over the dorsum of

hands followed by desquamation which starts from the periungual regions of hands and feet is a characteristic sign. These changes are seen in about 90% of children with KD. Later in the course of disease, Beau's lines may develop over the nails which are transverse ridges more easily felt than seen over the nails.

5. *Rash*: An erythematous, morbilliform, non-pruritic rash can occur which begins from the trunk and involves the perineal area. The rash is transient and fades by itself. The rash of KD can be polymorphous but is never vesicular. Reported to be present in more than 90% of affected children from developed countries, it may be difficult to perceive in children with dark skin.
6. *Lymphadenopathy*: Unilateral, tender, cervical lymphadenopathy occurs in about 60% of children with KD.

A diagnosis of KD can be made if a child with fever for more than 5 days fulfils four of the aforementioned five criteria. If a child has fever for less than 5 days or has less than four criteria, the presence of coronary artery abnormalities (CAAs) detected on 2D echocardiography would also suggest a diagnosis of KD [17].

The diagnosis of KD can be very challenging and it may test the clinical acumen of even the most astute physician. It must be clearly understood that as there is no gold standard for diagnosis of KD, one does not know the sensitivity and specificity of the diagnostic criteria for this condition [18]. From clinical experience, it is clear that if one applies the criteria very strictly, the specificity would be high, but this would be at the cost of sensitivity. There is no doubt whatsoever that many children with KD may not fulfil these criteria. Further, as the clinical spectrum of KD evolves over a few days, the clinical findings which may have been present during the first few days of the illness may no longer be evident subsequent in the course [19].

In addition to these characteristic features, some additional findings suggest the possibility of KD. Perianal desquamation which appears earlier than the periungual desquamation is also characteristic, and its presence should be looked for in every child having fever for more than

5 days. A transient arthritis may be seen in a quarter of the patients and may, at times, be the presenting feature of KD. Reactivation of the BCG scar can be noted in some infants with KD but this is extremely uncommon in our experience. Hydrops of the gallbladder may be seen during the acute phase of KD. Asymptomatic anterior uveitis is not uncommon during the first few days of the illness.

The clinical course in KD is divided into three phases [2, 13]:

Acute febrile phase: This lasts from the onset of illness to 10–14 days and is characterized by high-grade fever, irritability, rash, strawberry tongue, red cracked lips and limb changes. Signs of myocarditis may appear in this phase, which include tachycardia, S3 gallop and congestive cardiac failure.

Subacute phase: This lasts up to 4–6 weeks and ends with return of the acute phase reactants to normal. The CAAs first appear in this phase.

Convalescent phase: This lasts for months to years during which healing of the vessels occurs with remodelling and scarring. Beau's lines occur during this phase.

Incomplete KD

If a child does not fulfil the criteria and has less than four features, a diagnosis of incomplete KD is proffered. Incomplete KD is commonly seen in infants, and ironically this is the group of patients who are at highest risk for the development of CAA. The American Heart Association has suggested an algorithm for identification of children who do not fulfil the criteria for KD and are suspected to have KD and so have a risk of developing CAA [17].

Atypical KD

When a child with KD presents with features that are not usually seen in this condition, a diagnosis of atypical KD is proffered. Clinical features which are unusual in KD include, but are not restricted to, nephritis, seizures, acute

hepatitis, neurological obtundation or hypertension [13, 17].

Differential Diagnosis

Because of it being an acute febrile illness, the differential diagnosis of KD includes the common infectious illnesses of childhood:

Scarlet fever
 Measles
 HHV-6 and HHV-7
 Toxic shock syndrome
 Stevens-Johnson syndrome
 Drug hypersensitivity
 Serum sickness
 Systemic-onset juvenile idiopathic arthritis

Investigations

It cannot be overemphasized that there is no pathognomonic laboratory test for KD. However, there are several investigations which may support a clinical diagnosis of KD. A normocytic, normochromic anaemia with polymorphonuclear leucocytosis is usually seen. Thrombocytosis is characteristically seen after day 10 of fever, but thrombocytopenia can also occur, especially when there is an accompanying macrophage-activation syndrome. Acute phase reactants like the C-reactive protein (CRP) and the erythrocyte sedimentation rate are elevated during the acute phase. Sterile pyuria may be found which is of urethral origin; therefore, one may not obtain this finding if urine is obtained by suprapubic bladder aspiration. Pyuria in a sick and febrile child is liable to be misdiagnosed as a urinary tract infection [2, 3].

Ultrasonography may reveal hydrops of the gallbladder. The gallbladder may sometimes enlarge to the extent that it becomes palpable on physical examination. Cerebrospinal fluid examination is not indicated in KD. If, however, it has been carried out, one may see findings consistent with aseptic meningitis. Lipid abnormalities are not unusual in children with KD. Serum triglycerides and low-density lipoproteins are increased

and high-density lipoproteins are reduced. These abnormalities begin in acute phase and may take several months to normalize.

2D echocardiography remains the imaging modality of choice for evaluation of coronary artery abnormalities in children with KD. CAAs include ectasia and/or aneurysms in proximal parts of left main coronary artery, left anterior descending artery, left circumflex artery and/or right coronary artery. This examination needs to be carried out by a pediatric cardiologist or a physician who has the requisite training and experience in evaluation of coronary arteries. Coronary arteries are said to be dilated if the size is more than 1.5 times that of the adjacent segment. Coronaries with diameter of more than 3 mm in a child less than 5 years of age and more than 4 mm in older children are said to be dilated. It is preferable to use z-scores for evaluation of coronaries in children. The use of these z-scores makes the follow-up and comparison easier and more reliable.

Children with KD can also have several other findings on echocardiography. These include a decrease in ejection fraction (suggestive of myocarditis), mild valvular regurgitation, increased brightness of the coronary vessels and pericardial effusion. All of these are indicative of an ongoing inflammatory process.

Treatment

It is important to diagnose and treat KD expeditiously as delays in therapy can result in serious morbidity and occasional mortality. The mortality rate of acute KD at Chandigarh is approximately 0.8%. CAAs can develop in a quarter of untreated patients with KD.

Every child suspected to have KD should be admitted and evaluated so that close clinical observation can be carried out. It cannot be overemphasized that clinical findings in KD may change from day to day, and it is of the utmost importance that these be observed and recorded methodically.

Treatment of KD consists of intravenous immunoglobulin (IVIg) and aspirin started within the first 10–12 days of illness [2, 3, 20–23]. IVIg

is given as a single intravenous infusion of 2 g/kg. It is generally administered over 8–12 h, but the infusion must be started slowly so as to avoid occurrence of hypersensitivity reactions. IVIg has been found to be very effective if given within the first 10 days of onset of illness. In case, however, the child presents late and the acute phase reactants are still elevated or if there are CAAs on echocardiography, IVIg should still be administered. The response to IVIg is often dramatic, and the irritability, so characteristic of KD, often disappears within a few hours of initiation of the infusion. Fever defervescence usually occurs within 12–18 h. Administration of IVIg can, on occasions, be associated with significant adverse effects like headache and vomiting. These are thought to be secondary to a mild aseptic meningitis which is known to be associated with administration of IVIg. These can usually be managed quite easily with symptomatic treatment. Ensuring adequate hydration and a slow rate of infusion of IVIg is said to decrease the occurrence of these adverse effects [22–25].

Aspirin in anti-inflammatory doses (30–50 mg/kg/day) is started along with IVIg and is continued till the child becomes afebrile. Thereafter, aspirin is continued in antiplatelet doses (3–5 mg/kg/day) till a follow-up echocardiography is done and found to be normal at 6–8 weeks of illness. If CAAs are found in follow-up echocardiography, then aspirin needs to be continued for prolonged periods. Additional anticoagulation (with warfarin or low molecular weight heparin) may be required in children with large aneurysms. While therapy with IVIg and aspirin has dramatically reduced the occurrence of CAAs in KD, a small proportion of patients (approximately 3–5%) still go on to develop CAAs despite seemingly appropriate therapy having been administered.

Approximately 10–20% of patients with KD either do not respond or have a recrudescence of fever that recurs within 36 h of completion of IVIg infusion. Such patients are said to have refractory KD. Several Japanese investigators [22–24] have put forth risk scoring systems for predicting refractory KD. Ogata et al. [22, 23] showed that children who were predicted to be

IVIg resistant on the basis of one such scoring system showed earlier defervescence of fever when treated pre-emptively with a combination of IVIg and IV methylprednisolone as compared to the group given IVIg alone. The occurrence of CAAs was also less in the former group. Miura et al. [24] showed that IV methylprednisolone, when used along with IVIg in children with refractory KD, does lead to faster defervescence. The effect, however, is not long-lasting. Further, the incidence of development of CAAs is not significantly different in two groups, and the occurrence of adverse effects was significantly higher in the group treated with IV methylprednisolone plus IVIg.

It must be noted that these scoring systems do not seem to yield reliable results in populations other than Japanese and therefore may have limited utility in day-to-day clinical practice in other countries.

There is no consensus on the best modality for treatment of refractory KD. Therapeutic options include a repeat dose of IVIg, intravenous pulse methylprednisolone or anti-TNF α agents (e.g. infliximab). Cyclosporin and plasmapheresis have also been used in such circumstances [2, 3].

Children with KD who have no CAA or have only transient coronary artery ectasia require low-dose aspirin (3–5 mg/kg/day) for initial 6–8 weeks. Children with a single small coronary artery aneurysm should be given aspirin at least until the disappearance of aneurysm. However, in a child with giant coronary artery aneurysm, or one with multiple coronary aneurysms, long-term antiplatelet therapy along with antithrombotic therapy in the form of oral warfarin or low molecular heparin is mandated.

Risk Factors for the Development of CAA

Male sex	
Age less than 6 months	
Thrombocytopenia at presentation	
Neutropaenia, hyponatraemia and hypoalbuminaemia	
Prolonged fever or recrudescence of fever	
Failure to respond to IVIg	

Disease Course

A landmark study by Kato et al. [25] showed that up to 50% of small- to medium-sized aneurysms resolve on follow-up. Giant aneurysms (>8 mm size), however, do not resolve and are associated with significant long-term morbidity. Even when the coronary aneurysm appears to have resolved anatomically, functional vessel wall abnormalities are known to persist and may result in myocardial ischaemia/infarction later in life.

KD can be associated with significant long-term sequelae. This has been conclusively borne out through recently published long-term follow-up studies carried out at San Diego, USA [26]. It is obvious that KD is no longer considered to be merely a one-time disease of childhood. Considering the fact that the incidence of this disease is showing a steady increase in several countries, it is likely to emerge as the commonest cause for acquired heart disease in children the world over. Many of these children would grow up to be adults with coronary sequelae. KD, therefore, needs to be considered as a disease of public health importance, and health planners need to be made aware of these facts.

Take-Home Messages

1. KD is the most common cause of acquired heart disease in children in developed countries.
2. The incidence of KD varies across the world; the highest has been reported from Japan.
3. There is no gold standard for diagnosis of KD, it is to be considered in a child with prolonged pyrexia, irritability and sequential appearance of clinical signs of KD.
4. The management is with IVIg and aspirin. The latter is used initially in anti-inflammatory doses initially and then reduced to antiplatelet dose. The duration of treatment depends on the coronary artery involvement.
5. There are no clear guidelines for resistant KD, most centres would use a second dose of IVIg, and other choices are steroids and infliximab.

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