

Continuous Medical Education

Kawasaki disease: an update

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DEFINITION

The disease was first described by Dr. Tomisaku Kawasaki in 1967 in Japanese children where it continues to be the most prevalent¹. It is defined as:

1. An acute febrile vasculitis occurring most commonly in infants and children under 5 years of age.
2. Vasculitis, especially involving coronary arteries, which is a serious complication*.

ETIOLOGY

At present, the etiology of this panvasculitis remains unknown. Many etiological agents have been investigated and an infectious trigger, host immune response and genetic predisposition have been postulated. The infectious hypothesis is supported by findings such as seasonal occurrence of the disease (winter and early spring in the United States); however, the presence of infections at diagnosis of Kawasaki disease (KD) did not affect the patients' response to treatment and coronary artery outcome².

EPIDEMIOLOGY

Kawasaki disease is markedly more prevalent in Japan and in children of Japanese ancestry, with an annual incidence of about 112 cases per 100,000 children <5 years old³. In the United States, race-specific incidence rates derived from administrative data indicated that Kawasaki disease is most common among Americans of Asian and Pacific Island descent (32.5/100,000 children <5 years old), intermediate in non-Hispanic African Americans (16.9/100,000 children <5 years old) and Hispanics (11.1/100,000 children <5 years old), and lowest in whites (9.1/100,000 children <5 years old)⁴.

Rates of recurrence and familial occurrence of Kawasaki disease are best documented in the literature from Japan; these rates may be lower in other races and ethnicities. In Japan, the recurrence rate of Kawasaki disease has been reported to be about 3%. The proportion of cases with a positive family history is about 1%⁵.

In the United States, Kawasaki disease is more common during the winter and early spring months; boys outnumber girls by about 1.5 to 1.7:1; and 76% of children are <5 years old⁴. The

case fatality rate in Kawasaki disease in Japan is 0.08%⁵ compared to in-hospital mortality rate in USA of about 0.17%⁶.

HISTOPATHOLOGY

In the early stage, there is panvasculitis with increase in perivascular inflammatory cells, initially neutrophils and later macrophages and T-lymphocytes. There is inflammatory endothelial and subendothelial edema initially with later damage of the internal elastic lamina and development of aneurysms. The medial smooth muscle cells proliferate and eventually fibrosis begins with scar formation. The ongoing proliferation of the medial smooth muscle cells after their early degeneration in the acute stage of Kawasaki disease is responsible for the late stenosis of the coronary arteries⁷.

SIGNS AND SYMPTOMS

The symptoms of KD can be classified into two categories: principal symptoms and other significant symptoms or findings⁸.

Principal Symptoms

Fever: The fever typically is high spiking and remittent, with peak temperatures generally >39°C (102°F) and in many cases >40°C (104°F). In the absence of appropriate therapy, fever persists for a mean of 11 days, but it may continue for 3 to 4 weeks and, rarely, even longer. With appropriate therapy, the fever usually resolves within 2 days.

Extremities: Changes in the extremities are distinctive. Erythema of the palms and soles or firm, sometimes painful induration of the hands or feet, or both erythema and induration often occur in the acute phase of the disease. Desquamation of the fingers and toes usually begins in the periungual region within 2 to 3 weeks after the onset of fever and may extend to include the palms and soles. Approximately 1 to 2 months after the onset of fever, deep transverse grooves across the nails (Beau's lines) may appear.

Skin: An erythematous rash usually appears within 5 days of the onset of fever. The rash may take various forms; the most common is a nonspecific, diffuse maculopapular eruption. Occasionally seen are an urticarial exanthem, a scarlatiniform rash, an erythroderma, an erythema-multiforme-like rash, or, rarely, a fine

micropustular eruption. Bullous and vesicular eruptions have not been described. The rash usually is extensive, with involvement of the trunk and extremities and accentuation in the perineal region, where early desquamation may occur.

Eyes: Bilateral conjunctival injection usually begins shortly after the onset of fever. It typically involves the bulbar conjunctivae (sparing the limbus, an avascular zone around the iris) much more often than the palpebral or tarsal conjunctivae; is not associated with an exudate, conjunctival edema or corneal ulceration; and usually is painless. Mild acute iridocyclitis or anterior uveitis may be noted by slit lamp; it resolves rapidly and rarely is associated with photophobia or eye pain.

Lips & Oral Cavity: Changes of the lips and oral cavity include (i) erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips; (ii) a "strawberry tongue" that is indistinguishable from that associated with streptococcal scarlet fever, with erythema and prominent fungiform papillae; and (iii) diffuse erythema of the oropharyngeal mucosae. Oral ulcerations and pharyngeal exudates are not seen.

Lymph Nodes: Cervical lymphadenopathy is the least common of the principal clinical features. It is usually unilateral and confined to the anterior cervical triangle, and its classic criteria include ≥ 1 lymph node that is >1.5 cm in diameter. Imaging studies frequently demonstrate multiple enlarged nodes without suppuration⁹. The lymph nodes often are firm and nonfluctuant, are not associated with marked erythema of the overlying skin, and are nontender or only slightly tender. Occasionally, the lymph node swelling of Kawasaki disease can be confused with bacterial adenitis.

Because the principal clinical findings that fulfill the diagnostic criteria are not specific, other diseases with similar clinical features should be excluded

Other Symptoms or Findings of Significance

Cardiac Findings

Cardiovascular manifestations can be prominent in the acute phase of Kawasaki disease and are the leading cause of long-term morbidity and mortality. During this phase, the pericardium, myocardium, endocardium, valves, and coronary arteries all may be involved. Cardiac auscultation of the infant or child with Kawasaki disease in the acute phase often reveals a hyperdynamic precordium, tachycardia, a gallop rhythm, and an innocent flow murmur in the setting of anemia, fever, and depressed myocardial contractility

secondary to myocarditis. Children with significant mitral regurgitation may have a pansystolic regurgitant murmur that is typical of this condition. Occasionally, patients with Kawasaki disease and poor myocardial function may present with low cardiac output syndrome or shock. Electrocardiography may show arrhythmia, prolonged PR interval, or nonspecific ST and T wave changes.

Noncardiac Findings

Multiple noncardiac clinical findings may be observed in patients with Kawasaki disease. *Arthritis or arthralgia* can occur in the first week of the illness and tends to involve multiple joints, including the small interphalangeal joints as well as large weight-bearing joints. Arthritis or arthralgia developing after the 10th day of illness favors large weight-bearing joints, especially the knees and ankles. *Neurologic* Symptoms include irritability more than that observed in children with other febrile illnesses. Transient unilateral peripheral facial nerve palsy occurs rarely. Transient high-frequency sensorineural hearing loss (20 to 35 dB) can occur during acute Kawasaki disease, but persistent sensorineural hearing loss is rare¹⁰. *Gastrointestinal* complaints, including diarrhea, vomiting, and abdominal pain, occur in approximately one third of patients. Hepatic enlargement and jaundice can occur. Hydrops of the gallbladder can occur and can be identified by abdominal ultrasound¹¹. Erythema and induration at the site of a previous vaccination with Bacille Calmette-Guérin (BCG) is common in Japan, where BCG is used widely¹². *Rare* findings include testicular swelling, pulmonary nodules and infiltrates¹³, pleural effusions, and hemophagocytic syndrome¹⁴.

DIAGNOSIS

Complete Kawasaki disease

The Japanese classification for KD requires the presence of 5 of the following 6 criteria: characteristic fever, bilateral conjunctivitis, changes of lips and oral cavity, polymorphous exanthema, changes of peripheral extremities and cervical lymphadenopathy. The American classification differs in that fever plus 4 of the remaining 5 criteria are required¹⁵.

Two modifications were made (Table 1)¹⁶. The presence of perineal desquamation was added to the criterion describing changes in the extremities. In acknowledgement of the importance of coronary artery disease in defining KD¹⁵, it was agreed that in the presence of fever and coronary arterial involvement demonstrated by

echocardiography, fewer than 4 of the remaining 5 (the number not yet defined) are needed to classify a patient as having KD. On the other hand irritability, which was suggested as a new criterion in the first survey was not accepted by the consensus group since it was too non-specific. There are very rare patients without fever and this should be kept in mind.

<p>Table 1. Classification criteria for Kawasaki Disease</p> <p>Fever persisting for at least 5 days (mandatory criterion) plus 4 of the following 5 should be present:</p> <ol style="list-style-type: none"> 1) Changes in peripheral extremities or perineal area 2) Polymorphous exanthema 3) Bilateral conjunctival injection 4) Changes of lips and oral cavity: injection of oral and pharyngeal mucosa 5) Cervical Lymphadenopathy <p>In the presence of coronary artery involvement detected on echocardiography and fever, fewer than 4 of the remaining 5 criteria are sufficient (exact number of criteria required to be defined in the validation phase).</p>

(Quoted from Newburger et al, 2004)¹⁵.

Disease other than KD should be considered if the fever persists and the laboratory and the echocardiography criteria are not fulfilled or if there is exudative conjunctivitis, exudative pharyngitis, discrete oral lesions or ulcers, bullous or vesicular rash, or generalized lymphadenopathy¹⁵.

Incomplete Kawasaki disease

About 10% of the patients, especially infants, do not fulfill all the criteria to make the diagnosis of complete KD. Incomplete KD is not a milder form of the disease and the children with incomplete KD have similar risk of coronary artery abnormalities and laboratory findings as the children with complete KD. Figure (1) showing an algorithm for evaluation of suspected incomplete Kawasaki disease¹⁷.

Differential diagnosis of KD should include viral infections, scarlet fever, staphylococcal scalded skin syndrome, toxic shock syndrome, bacterial cervical lymphadenitis, drug hypersensitivity reactions, Steven-Johnson syndrome, rheumatic fever, juvenile rheumatoid arthritis, Rocky Mountain spotted fever, leptospirosis and acrodynia¹⁵. It should also be included in the differential diagnosis of fever of unknown origin in children. Differential diagnosis

of undiagnosed KD must be considered in young adult patients with aneurysms and early atherosclerotic lesions without significant family history or risk factors for early atherosclerosis¹⁷.

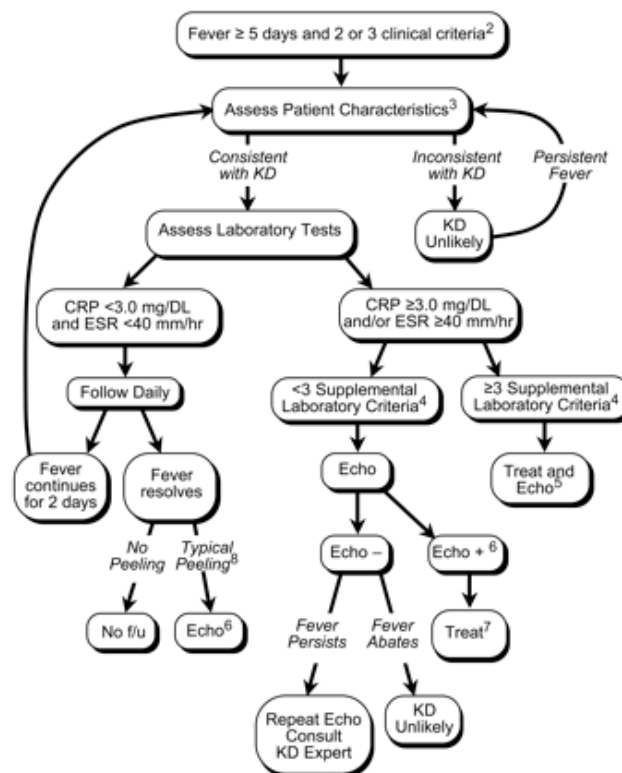


Figure 1. Evaluation of suspected incomplete Kawasaki disease.

INVESTIGATIONS

Laboratory tests

Leucocytosis with elevated neutrophils, marked thrombocytosis (rarely thrombocytopenia), normocytic normochromic anemia, and elevated acute phase reactants ESR and CRP are all seen in KD. Mild hypoalbuminemia, mild increase in serum transaminases, and sterile pyuria may be seen. These findings gradually decrease after therapy with immunoglobulins. Elevated acute phase reactants CRP ≥3mg/dl or ESR ≥40mm/h is consistent with KD. There are 6 diagnostic supplemental laboratory criteria include albumin ≤ 3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 d ≥450 000/mm³, white blood cell count ≥15000/mm³, and urine ≥10 white blood cells/high-power field. A throat culture, antistreptolysin-O titer and evaluation of other diseases that can mimic KD must be made prior to immunoglobulin therapy. About 4-6 weeks of onset of illness, a complete blood count with differential, CRP and ESR are recommended. Lipid profile should be evaluated at one year follow-up and periodically thereafter¹¹.

Electrocardiogram

Sinus tachycardia is present due to the fever. Nonspecific ST-T wave changes and low voltage QRS complexes may be observed in presence of pericarditis. Prolongation of PR and QT interval may also occur. Myocardial ischemic changes and arrhythmias may also occur in case of coronary artery occlusion.

Echocardiogram

Visualization of branches of coronary arteries by 2-D ultrasound and measurement of the proximal internal luminal diameters is extremely crucial in this disease and may require sedating the patient. It is recommended at the time of diagnosis, at 2 weeks and then 6 weeks after the onset of disease. Late follow-up echocardiograms are based on the severity of the disease. For a positive echocardiogram, either a coronary artery aneurysm or ectasia needs to be demonstrated.

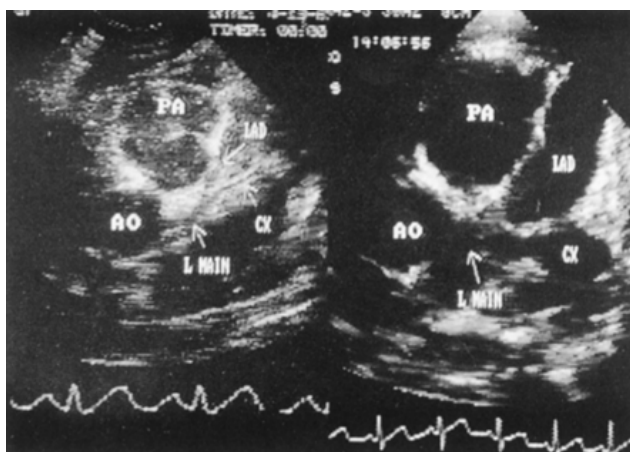


Figure 2 . 2D echocardiogram. AO indicates aorta; PA, pulmonary artery; LAD, left anterior descending coronary artery; CX, circumflex coronary artery; and L MAIN, left main coronary artery¹⁷.

Coronary Angiograms

Cardiac catheterization with coronary angiography not only allows for detection of distal coronary aneurysms not seen by echocardiogram and coronary artery obstruction with either a thrombus or stenosis, but also allows for therapeutic options such as intraluminal thrombolytic therapy for a thrombus or percutaneous transluminal coronary angioplasty (PTCA) for stenosis¹⁸. Catheterization is indicated at about 6 to 12 months after onset of KD (or earlier if necessary) in patients with aneurysms.

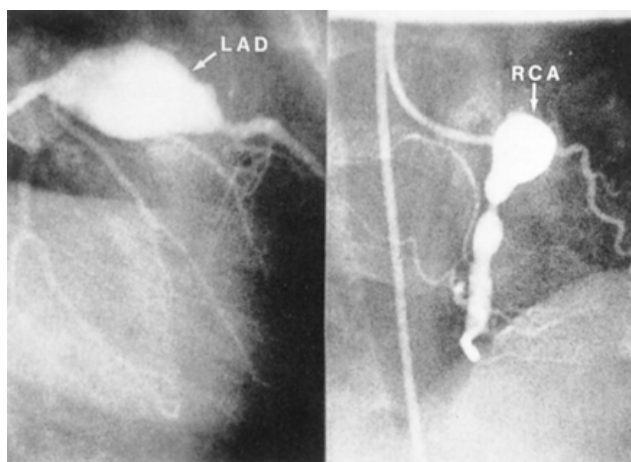


Figure 3 . Coronary angiogram demonstrating giant aneurysm of the LAD with obstruction and giant aneurysm of the RCA with area of severe narrowing in 6-year-old boy¹⁷.

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)

The advantage of MRI and CT imaging modalities is the non-invasive nature of both these excellent techniques that can supplement other studies. These modalities together are helpful in the detection of distal aneurysms, intravascular changes such as thrombi, occlusion, intimal hypertrophy and calcification, and also help detect involvement of arteries other than coronary blood vessels¹⁹.

RISK FACTORS FOR DEVELOPMENT OF CORONARY ANEURYSMS

The peak incidence of development of aneurysms is 2 to 6 weeks after onset of the disease. Over the past 3 decades several risk factors have been identified that are associated with higher incidence of coronary artery aneurysm formation. These include, family history of KD, age less than one year, male gender²⁰, fever longer than 14 days duration or double spiking fever, hemoglobin concentration <10g/dL or hematocrit <35%, white cell count >30,000/mm³, platelet count <350,000/mm³ ²¹ ESR (Westergren) >101 mm/hour, serum sodium level <135mEq/L, and serum albumin <3 g/L²⁰. Based on the above laboratory values, various scoring systems have been developed to predict the risk of developing aneurysm but these have not been validated.

ACUTE MANAGEMENT

Acetylsalicylic acid (ASA) therapy

High dose ASA is started at 80-100 mg/kg/day in four divided doses and is continued for 48 to 72 hours after cessation of fever. Gastritis may develop and hence ASA is given preferably with meals. After high dose, low dose ASA (anti-platelet dose) at 3-5 mg/kg/day is begun and continued till 2 months after onset of disease until demonstration that there is no evidence of coronary abnormalities on echocardiogram. If coronary abnormalities are detected, low dose ASA is continued indefinitely. Ibuprofen should be avoided in these children who are on ASA as it antagonizes the platelet inhibition induced by ASA. Reye syndrome has been reported in KD children on ASA and hence ASA should be withheld on exposure to either influenza or varicella. Patients may be annually vaccinated with influenza vaccine (hold ASA and switch to another antiplatelet agent for 6 weeks after vaccine)¹⁷.

Intravenous Immunoglobulin (IVIG) therapy

A single infusion of IVIG is given at a dose of 2 g/kg in addition to ASA in the acute phase within 10 days of onset of fever. It may be given even after 10 days of onset of the disease if fever persists or aneurysms develop or elevated ESR/CRP are present.¹⁵ Early treatment with IVIG within 5 days of illness has been associated with need for IVIG retreatment²¹. The exact mechanism of action by which IVIG reduces the prevalence of coronary artery abnormalities and acute phase reaction is not known. A number of mechanisms may be at play, including decreasing cytokine production²², blockade of the Fc receptors, neutralization of antigens, reversal of immunoregulatory abnormalities with increase in suppressor T cells and decrease in B lymphocytes and inhibition of complement-mediated lysis. The use of IVIG for treating KD though is the best available therapy, is not an ideal form of therapy; despite adequate treatment, nearly 5% of the children develop transient coronary dilatation and 1% giant coronary aneurysms. In addition IVIG is a blood product and carries with it risk of allergic reactions such as serum sickness and the risk of blood borne pathogens. Live vaccines should be deferred for 11 months after IVIG therapy²³.

Other therapies

Steroid therapy in early phase of KD is currently under trial. More recently there has been an interest in use of abciximab²⁴ in those with large

aneurysms. Therapy with anti-cytokine agents such as infliximab²⁵ and pentoxifylline²⁶ has also been reported.

Immunoglobulin resistant kawasaki syndrome

Failure to respond to IVIG therapy with persistent fever or reappearance of fever 36 hours of completion of infusion constitutes immunoglobulin-resistance and is seen in about 10% of the cases. The risk of developing coronary artery lesions in this population is as high as 10%, while in those who respond to IVIG, it is about 1%. This refractoriness may reflect a genetic variation of the patient population, or variability in the agent causing KD or it may be the quantity of the "anti-inflammatory factor" in the IVIG which can vary from one pool to the other²⁷. A second, third or even a fourth dose of IVIG maybe needed to quell the inflammatory cascade. Three factors seen in association with immunoglobulin resistant KD are: CRP > 10 mg/dL, lactate dehydrogenase > 590 IU/L and hemoglobin concentration < 10 g/dL²⁸. If fever persists after 3-4 doses of IVIG, pulsed steroid therapy²⁹ may be initiated using intravenous methylprednisolone 30 mg/kg over 2 hours once daily for 1 to 3 days and then tapered. The risks associated with this therapy commonly include leucocytosis, hyperglycemia and hypertension and rarely seizures. Intravenous heparin should be given along with methylprednisolone, especially in those with coronary artery lesions since steroids may increase thrombogenicity. An alternative low dose steroid regimen used in some centers is intravenous methylprednisolone with 2 mg/kg/day divided in 3 doses for one day followed by tapering dose of oral prednisone 2mg/kg/day over 6 weeks. Some centers are routinely using infliximab²⁵ for refractory KD although the therapy is still experimental. Other reported therapeutic modalities include plasma exchange³⁰, cyclophosphamide²⁷, cyclosporine A³¹ and ulinastatin³². Whichever therapy is used, patient should periodically be monitored for progression of coronary artery lesions by echocardiography and signs of continuing inflammation with CRP and/or ESR.

Prevention and management of coronary artery thrombosis

Once the coronary artery aneurysm is identified, it is important to prevent thrombosis in the aneurysm due to anatomical, hematological and immunological factors; all these factors together put these children at high risk for forming a

thrombus, leading to coronary artery occlusion. The anatomical factors are sluggish blood flow in a dilated segment, development of stenosis at the inlet of the aneurysm and proximal or distal coronary obstruction. Significant increase in the number of platelets in the acute and subacute phase may also contribute to thrombosis. The immunological factors include activation of platelets and endothelium, making blood hypercoagulable. In these patients antiplatelet therapy is recommended for at least until the lesion regresses. In addition to antiplatelet therapy, anticoagulation is recommended in those children with multiple or complex aneurysms or those with single aneurysm = 6 mm in size¹⁵.

Antiplatelet therapy

The most prevalent antiplatelet therapy is with ASA at 3-5 mg/kg/day. Clopidogrel or dipyridamole may be given in addition to ASA to suppress platelet activation in high risk patients. Clopidogrel alone has also been recommended in KD when ASA is not tolerated or is contraindicated³³.

Anticoagulant therapy

Initiation of intravenous unfractionated heparin is done until warfarin dose leads to therapeutic levels with international normalized ratio (INR) of 2 to 2.5. Warfarin can be replaced with low molecular weight heparin (target antifactor Xa level of 0.5 - 1.0 U/mL), especially in infants where monitoring for INR is difficult or in pregnant females where it is contraindicated.

Fibrinolytic therapy

Either intravenous or direct intracoronary infusion³⁴ via catheterization of a fibrinolytic agent is indicated to restore patency of the coronary artery. Streptokinase, tissue plasminogen activator or urokinase may be used in addition to ASA and heparin therapy.

Platelet glycoprotein IIb/IIIa inhibitor

This agent inhibits platelet aggregation and has been found to lower rates of reocclusion and reinfarction in adults with coronary artery disease when given along with fibrinolytic therapy³⁵. Abciximab has been reported to enhance vascular remodeling and hasten reduction of aneurysm size²⁴.

Mechanical intervention

Restoration of patency of the coronary artery in the acute setting can also be achieved with angioplasty with or without stent placement³⁶.

MANAGEMENT IN THE LATE PHASE; RISK OF ATHEROSCLEROSIS

Low risk children, those without coronary artery abnormalities or those who had complete resolution of transient ectasia within 2 months of onset of KD may discontinue the ASA and return to normal physical activity. No invasive testing is recommended in these children but they should be assessed and counseled for atherosclerotic risk every 3 to 5 year intervals¹⁵. In those with coronary aneurysms (high risk patients), physical activity beyond 2 months of acute KD, especially in the older children (>11 years), should be guided by stress tests/ perfusion scans. Contact sports should be avoided. Annual (twice a year if ≥ 6 mm aneurysm or multiple aneurysms) cardiovascular risk assessment should be performed with assessment of risk factors for premature atherosclerosis, echocardiogram, ECG, stress test/myocardial perfusion scan. Angiography is indicated if ischemia is detected on noninvasive testing. Beta-blockade therapy is recommended to reduce myocardial oxygen consumption in those who have coronary artery obstruction¹⁵. The loss of endothelial vasoreactivity, ongoing vasculitis, and a proatherogenic lipid profile are probable risk factors for accelerated atherosclerosis that may lead to premature atherosclerosis and ischemic heart disease in this population. Thus KD population should be monitored at regular intervals for risk factors for atherosclerosis especially in those with prior history of coronary aneurysms. Weight management and avoidance of smoking, sedentary lifestyle and high cholesterol foods should be stressed. Periodic evaluation of blood pressure, lipid profile and adiposity should also be made¹¹.

SUMMARY

The hallmarks of KD are involvement of systemic blood vessels along with inflammation and endothelial activation, acute phase reaction, marked immune activation and increased thrombogenicity. The etiology of KD remains unknown. Recognition of the disease and its early treatment are of paramount importance for avoiding coronary artery complications. When diagnosed and treated early with high dose intravenous immunoglobulin, 95% of the patients have a mild course without coronary artery aneurysm formation and negligible occurrence of early acute myocardial infarction. However, despite therapy about 20% patients develop ectasia and 6% develop coronary aneurysms.

Immunoglobulin resistance and incomplete form of KD continue to remain challenging problems. Damage of the coronary vasculature in Kawasaki disease appears to have long-term sequelae, necessitating life long monitoring even after aneurysms have regressed.

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