Current Perspectives on Kawasaki Disease

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Abstract. The etiology of Kawasaki disease (KD) remains unknown despite several years of dedicated research in this direction. Recently coronavirus infection and genetic polymorphisms have been implicated. Since first description of the disease there have been few changes in the diagnostic criteria except for newer recommendations of fever of at least 4 instead of 5 days duration. Recently, Echocardiography Criteria and Laboratory Criteria have been added to aid in the diagnosis of incomplete KD where all the historical diagnostic criteria are not present; this is now called the "incomplete form of KD" as opposed to "atypical form of KD". The word "atypical" is reserved for unusual presentations of KD such as those with hemophagocytic syndrome or nerve palsy. The treatment of KD includes infusion of high dose immunoglobulin. Patients non-responsive to immunoglobulin therapy are labeled as having "immunoglobulin resistant KD". The treatment of immunoglobulin resistant KD can be challenging and new therapies that have tried with some success. Late outcomes after 4 decades of treating these patients have recently been published. There has been some concern about increased risk for premature atherosclerosis in patients with childhood KD who had coronary artery abnormalities. **[Indian J Pediatr 2005; 72 (7) : 621-629]**
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Kawasaki disease (KD) is an acute systemic vasculitis with predilection for coronary arteries and potential for aneurysm formation. The disease was first described by Dr. Tomisaku Kawasaki in 1967 in Japanese children where it continues to be the most prevalent.[1] It is a major pediatric disorder and is becoming a leading cause of acquired heart disease in children in many nations because the incidence of acute rheumatic fever is decreasing. Availability of echocardiography and awareness of the KD by the physicians has also made an impact on early detection and treatment of this disease. KD should 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 atherosclerosis.[2,3]

The purpose of this paper is to present a review of the etiology, clinical features and treatment of KD with an emphasis on the current state of the art.

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), with endemic and epidemic outbreaks and low incidence of KD in infants before 3 months of age when maternal antibodies are present or after 8 years of age when immunity to various organisms has developed. The portal of entry may be respiratory tract,[4] gastrointestinal tract[5] or skin.[6] Various infectious agents have been detected in children with KD, including leptospira, Yersinia pseudotuberculosis, chlamydia, parvovirus B 19, Epstein-Barr virus and most recently, coronavirus.[7]

Immunocompromised patients such as those with human immunodeficiency virus[8] or chickenpox infection [9] have increased incidence of KD. Bacteria which produce toxins act as superantigens; streptococcus and staphylococcus have also been detected in children with KD,[10-14] but not at a higher incidence than that seen in other febrile children.[14] In addition, children with KD have similar ability to mount antibody response to toxins when compared those children without KD unlike the women with toxic shock syndrome who have a defective serological response to toxic shock syndrome toxin-1 and hence develop the toxic shock syndrome.[15]

Genetic predisposition is hypothesized; the risk of occurrence increases with family history of KD (1%) with an increased risk in a twin to about 13%.[16] Genetic polymorphisms of vascular endothelial growth factor and its receptors, CD40 ligand and angiotensin-1 converting enzyme have all been implicated in coronary artery aneurysms formation in KD.[17-19]

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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 artery.[20]

INFLAMMATION AND REMODELING IN CORONARY VESSELS

Acute vascular inflammation and marked immune activation are hallmarks of this disease. There is activation of the endothelium with an increase in levels of several proinflammatory cytokines.[21,22] The serum level of sE-selectin, a soluble cell adhesion molecule, is increased as a result of activation of endothelial cells.[23,24] In the presence of inflammation, tissue destructive enzymes such as elastases, matrix metalloproteinases and collagenolytic cysteine proteases increase in KD and are involved in the breakdown of internal elastic lamina and vascular wall remodeling.[25,26] With progression of vascular injury, serum and tissue cystatin C (which exerts a protective role in vascular remodeling) levels can get severely depressed and significantly lower serum levels have been seen in patients with dilated aortas[27] and in acute KD[28] It appears that macrophages play an important role in producing vasculitis through this mechanism of release of proteolytic enzymes. Is it possible that the decrease in macrophage activity after immunoglobulins,[29] with subsequent decrease in elastolytic proteases is the key to the therapy of KD? There is a rapid decrease in pro-inflammatory cytokines immediately after immunoglobulin infusion[21] and this may be a mechanism by which the symptoms improve within hours of infusion.

SIGNS AND SYMPTOMS

KD is an acute febrile illness in childhood, mostly seen in children younger than 5 years of age with male predominance (male to female ratio is 1.5:1). The fever is usually high spiking and persistently recurring for several weeks if not treated.[30]

Skin

A diffuse erythmatous rash occurs that can be macular, maculo-papular, or rarely micropustular. The rash mimics other disease entities and may appear urticarial, erythema-multiforme-like or like "sand-paper rash" of scarlet fever. The rash is present over extremities, trunk and in the perineal region. In the subacute phase there is desquamation seen in the perineal and periungual region. Re-inflammation of the Bacille Calmette-Guerin inoculation site can occur and the site becomes indurated and erythematous.[31]

Head and neck

There is non-purulent bulbar conjunctivitis and parents usually describe a "pink eye". A large firm, nonfluctuant cervical or inguinal mass can occur due to lymphadenitis and is usually a conglomeration of multiple smaller lymph nodes.[32] The lips may initially become erythematous and swollen; later fissuring, peeling, cracking and bleeding may occur. Oral mucosa may also become erythematous as well. The tongue becomes erythematous and appears like a "strawberry tongue" similar to that seen in scarlet fever.

Extremities

Initially, swelling of the palms and soles may occur along with erythema and tenderness. Raynauds phenomenon and peripheral gangrene has also been described in KD. Arthralgia and arthritis, both pauciarticular and polyarticular, can also occur involving the small and large joints. In the subacute stage of KD, periungual peeling of toes and fingers is seen. Beau's lines or transverse grooves across nails may occur in this stage.

Cardiovascular

KD causes pancarditis with vasculitis being the major component. The endocardium, myocardium and pericardium are less severely involved. The coronary arteries are predominantly involved and obstruction of these vessels is responsible for majority of cardiac symptoms. Other blood vessels, such as iliac, axillary arteries can also be involved occasionally. Unless the coronary vessels are obstructed, the cardiac findings are mild and usually transitory with tachycardia due to fever and/or myocarditis, gallop (myocarditis), pericardial rub and distant heart sounds (pericardial effusion) and a new murmur from mitral regurgitation or aortic insufficiency.

Gastrointestinal

Patient usually complains of abdominal pain and may have anorexia. Mild dysfunction of the liver may occur with hepatomegaly and jaundice. Hydrops of the gall bladder, vomiting and diarrhea and paralytic ileus may occur. Occasionally, KD can mimic acute surgical abdomen, especially in older children.[33]

Neurological

The patients are extremely irritable due to aseptic meningitis that is present in significant number of children. Seizures and loss of consciousness may occur. Occasional sensorineural hearing loss[34] and facial nerve palsy [35] have been described which are usually not permanent.

Genitourinary

Testicular swelling and tenderness, urethritis and meatitis may occur. Sterile pyuria can also be present with increased leucocytes in urinary sediment. Late renal artery stenosis after aneurysmal dilatation can lead to systemic hypertension in these children.

Pulmonary

Cough and tachypnea may occur due to pneumonitis with pulmonary infiltrates and effusions.

DIAGNOSIS

Complete Kawasaki disease

Fulfillment of 5 out of the 6 clinical criteria (Table 1) is considered diagnostic of Kawasaki disease.[30] All patients must have fever of at least 5 days;[30] newer recommendations are fever of at least 4 days duration[36] In addition, at least 4 of the 5 criteria are needed for diagnosis of KD (Table 1). Not all the symptoms develop simultaneously and it may take few days for syndrome to develop. Hence, these patients should be assessed repeatedly. KD is diagnosed when patient has fever of unknown origin and no other source for fever, exanthems etc are present. Family history of KD or symptoms suggestive of KD should be considered a risk factor for KD.

Table 1. Diagnostic Clinical Criteria for Kawasaki Disease

Clinical Criteria
1. Fever of at least 5 days duration.
2. Polymorphous exanthema
3. Bilateral bulbar conjunctiva injection
4. Oral cavity and lip changes.
5. Changes in the extremities with swelling of palms and soles (membranous desquamation in the convalescent stage)
6. Cervical lymphadenopathy of greater than 1.5 cm diameter.

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. Diagnosis of incomplete KD can be difficult and in patients who have had a fever of 5 or more days, an echocardiogram showing coronary artery dilatation may clinch the diagnosis. If no coronary artery dilatation is present or if no echocardiogram has been performed but there is elevated erythrocyte sedimentation rate (ESR) to ≥ 40 mm/hr and/or C-reactive protein (CRP) ≥ 3 mg/dl and ≥ 3 of the 6 supplemental laboratory criteria are present (Table 2) diagnosis of incomplete form of KD is made.[36] 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 lymphadenopathy.[36] Differential diagnosis of viral infections, scarlet fever, staphylococcal scalded skin syndrome, toxic shock syndrome, bacterial cervical lymphadenitis, drug hypersensitivity reactions, Steven-Johnson syndrome, juvenile rheumatoid arthritis, Rocky Mountain spotted fever, leptospirosis and acrodynia must be kept in mind.[36]

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. There are 6 diagnostic supplemental laboratory criteria (Table 2).[36] 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 is recommended. Lipid profile should be evaluated at one year follow-up and periodically thereafter.

Table 2. Laboratory Criteria for Diagnosis of Incomplete Kawasaki Disease

Supplemental Laboratory Criteria
1. Serum albumin of ≥ 3 g/dL
2. Anemia for age
3. Elevation of alanine aminotransferase
4. Elevated platelets after 7 days of ≥ 45, 000/mm^3,
5. Elevated white blood cell count of ≥ 15,000/mm^3
6. Urine with ≥ 10 white blood cells/high-power field

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. The number and location of these coronary dilatations need to be recorded. Coronary artery aneurysms are considered small if they

are <5 mm, medium if between 5 to 8 mm and giant if > 8 mm.[30] The aneurysms are considered saccular if axial and lateral diameters are nearly equal and fusiform if symmetric dilatation with gradual tapering is seen. Coronary artery ectasia is considered when the vessel is dilated without a segmental aneurysm formation. The Japanese Ministry of Health criteria consider ectasia if the vessel is > 3mm in children < 5 years age or > 4 mm in children ≥ 5 years age or if the segment measures = 1.5 times greater than adjacent segment or if there is irregularity in the lumen.[37] Recent guidelines based on z-score values with values ≥ 2.5 considered abnormal have been developed based on body surface area of the child.[38] Attention to details such as perivascular echogenicity, intraluminal changes with linear shadows due to intimal thickening and absence of normal tapering of coronary arteries should also be given. The 2-D ultrasound imaging is also used to detect intraluminal thrombi, left ventricular wall motion abnormalities and pericardial effusion. Color flow Doppler is used to detect the flow in the coronary arteries and valvular insufficiency. Both 2-D and M-mode may be used to detect decrease in systolic function of the left ventricle and aortic root dilatation.[39] Presence of 3 or more of the 6 supplemental echocardiographic criteria is a condition under which diagnosis of KD can be made in absence of ectasia or aneurysms (Table 3).[36]

Table 3. Echocardiography Criteria for Diagnosis of Incomplete Kawasaki Disease

Supplemental Echocardiographic Criteria
1. Perivascular brightness
2. Z-scores of left anterior descending or right coronary artery between 2 and 2.5
3. Lack of vessel tapering
4. Decreased left ventricular function
5. Mitral regurgitation
6. Pericardial effusion

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 stenosis.[40] An aortogram is also indicated if it is the first study in a patient to detect involvement of other blood vessels and aneurysm formation. Catheterization is indicated at about 6 to 12 months after onset of KD (or earlier if necessary) in patients with aneurysms.

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 vessels.[41-45]

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,[46,47] male gender,[47] fever longer than 14 days duration or double spiking fever, hemoglobin concentration < 10g/dL or hematocrit < 35%,[48] white cell count > 30, 000/mm^3, platelet count < 350, 000[48-50] ESR (Westergren) > 101 mm/hour, serum sodium level < 135 mEq/L,[51] and serum albumin < 3 g/L.[47,48] 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[52-54] 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).

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 after10 days of onset of the disease if fever persists or aneurysms develop or elevated ESR/CRP are present.[36] Early treatment with IVIG within 5 days of illness has been associated with need for IVIG retreatment.[55,56] 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 production,[21] 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 therapy.

Other therapies

Steroid therapy in early phase of KD is currently under trial. More recently there has been an interest in use of abciximab in those with large aneurysms. Therapy with anti-cytokine agents such as infliximab and pentoxifylline 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 other. 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 < 10g/dL.[57] If fever persists after 3-4 doses of IVIG, pulsed steroid therapy[58,59] 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 methypredinsolone 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 infliximab[60] for refractory KD although the therapy is still experimental. Other reported therapeutic modalities include plasma exchange,[61] cyclophosphamide,[62] cyclosporine A[63] and ulinastatin.[64] 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 size.[36]

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 contraindicated.

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 infusion[65-67] *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 therapy. Abciximab has been reported to enhance vascular remodeling and hasten reduction of aneurysm size.[68]

Mechanical intervention

Restoration of patency of the coronary artery in the acute setting can also be achieved with angioplasty with or without stent placement.[69]

MANAGEMENT OF CORONARY ARTERY STENOSIS

Cardiac catheterization with intervention

Intervention with PTCA, rotational ablation and stenting have been performed with some success in KD children who have stenosis of the coronary or renal arteries. A catheter intervention is recommended in those with ischemic symptoms and those without ischemic symptoms but with reversible ischemia on stress test or with ≥ 75% stenosis in the left anterior descending coronary artery.[70] Angioplasty in lesions that are more than 2 years after the acute phase of KD is less successful.[71,72] Early detection of coronary artery stenosis and intervention with PTCA when the fibrosis is minimal and the lesion has not yet calcified may be optimal management in KD. For older stenotic lesions that are stiff and calcified, use of low pressure balloon and stent placement is recommended to prevent neoaneurysm formation. If PTCA cannot be achieved with balloon pressure of < 10 atm, rotational ablation or coronary artery bypass graft (CABG) surgery is indicated.[72-74]

Coronary revascularization surgery

CABG procedure is recommended for patients with reversible ischemia in association with long-segment stenosis, ostial stenosis, multiple stenosis, severe occlusion of left main coronary artery or left anterior descending coronary artery, severe occlusion of the greater than one major coronary artery, collateral coronary arteries in jeopardy, recurrent myocardial infarction or severe left ventricular dysfunction.[36] Most stenotic lesions occur in the proximal segments of the coronary vessels and hence graft sites are easily accessible. Arterial grafts are preferred to venous graft due to their growth potential and longer patency rates.

Cardiac transplantation

This is offered to those who have severe, irreversible ischemia with lesions that have not improved after catheter intervention or after CABG.[75]

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 intervals.[36]

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.[36] 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 obstruction.[36]

It has been speculated that coronary microvascular lesion may be the underlying factor of persistent sequelae in KD.[76] There is loss of endothelial reactivity in patients after an episode of Kawasaki disease indicating an enhanced stiffness of the coronary vessels.[77,78] Alteration in lipid profile has also been found in these patients many years after the disease.[79-81] It has been suggested that the damage of the coronary endothelial cells persists in Kawasaki disease, regardless of angiographic coronary sequelae, as assessed by plasma levels of thrombomodulin in coronary venous blood.[82] Cartilaginous metaplasia of the coronary arterial wall in long term survivors of Kawasaki disease is manifest as "ring calcifications".[83] There is a growing belief that carotid intima-media thickness (CIMT) on an echocardiogram can be regarded as an indicator of generalized atherosclerosis and increase in CIMT has been detected in KD.[84] Measurement of ultrasensitive CRP, a marker of acute phase reaction, is helpful in detecting ongoing inflammation in any tissue of the body with increased levels detected in KD many years after the disease.[85] 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. Atherosclerosis is a non-specific response of the blood vessels to chronic injury that may be of infectious or immune etiology. It is a proliferative response that is regulated by the endothelium and mediated by nitric oxide. Postmortem studies have demonstrated that the inflammatory insult to the endothelium and coronary artery wall creates a focus for subsequent accelerated atherosclerosis.[86] 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 made.

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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