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An Update on Kawasaki Disease Indian Perspective

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Abstract

Kawasaki Disease (KD) is an acute self-limiting systemic vasculitis of unknown origin. Circulating immune complexes, triggered by infectious agents, bacteria, or viral or other unknown cause, have been detected in the early phase of KD, implicating that immunopathologic mechanisms might be involved in the pathogenesis of vasculitis in KD.

Thrombocytosis with periungual peeling can almost make diagnosis of KD. In difficult situations supplementary criteria to be followed and early detection of Kawasaki disease is essential to start Immunoglobulin therapy even with add on newer medications to prevent ultimately coronary artery disease. Long management of coronary artery aneurysms will be followed up with lifelong antiplatelet and anticoagulant medications.

Keywords: Kawasaki Disease; Giant Coronary Artery Aneurysm; Immune Complex Vasculitis

Introduction

Kawasaki disease (KD) is an acute self-limiting systemic vasculitis of unknown origin. This was defined as mucocutaneous lymph node syndrome by Dr.Tomisaku Kawasaki in Japan and had characterized the complex pattern of this illness in 50 cases in 1967. It has been found to be the leading cause of paediatric acquired cardiac disease worldwide, especially in developed countries [1,2]. Coronary Artery Lesions (CALs) with aneurysmal dilation, thrombosis, and/or stenosis, leading to myocardial infarction and death, have been recognized as the most severe complication [3,4]. Circulating Immune Complexes (ICs), triggered by infectious agents, bacteria, or viral or other unknown cause, have been detected in the early phase of KD, implicating that immunopathologic mechanisms might be involved in the pathogenesis of vasculitis in KD [5-8]. Attempts to produce coronary vasculitis have been made in mice, weanling rabbits, and guinea pigs by injecting infectious agents, foreign proteins, horse serum and Lactobacillus casei cell walls [9,10]. Among the animal models, swine may be the unique and promising animal for biomedical research, especially in the field of cardiovascular diseases [11,12]. Recent advances in genetic analysis are contributing to the newer modalities in management of KD and improving our understanding of pathogenesis in KD.

Epidemiology

Almost 12000 new cases are detected every year in Japan and coronary artery lesions. According to recent epidemiologic studies, Asian populations have a much higher incidence of KD [13,14]. Japan has the highest annual incidence in the world (137.7 per 100 000 children < 5 years of age between 1999 and 2002), followed by Korea (105 per 100 000 children < 5 years of age between 2003 and 2005), and Taiwan (66 per 100 000 children <5 years of age between 1996 and 2002. Beijing has reported an increased incidence, increasing from 40.9 per 100 000 persons in 2000 to 55.1 in 2004, compared with the increase from 18.2 to 30.6 per 100 000 that occurred there between 1995 and 1999. In Hong Kong, the average annual incidence was 39 per 100 000 between 1994 and 2000.6 In Western countries, the incidence of KD is significantly lower. Canada reported an annual incidence of 20.6 per 100 000 for the period between 1998 and 2007. The United States had an annual incidence of 17.1 per 100 000. Almost 12000 new cases are detected every year in Japan and also coronary artery lesions after 30 days of illness showed only 3% only in Japan. Decreasing trend indicates that almost all KD cases were receiving IVIG as first line therapy. We must admit seriously that we do not have sufficient data to present the epidemiology in India till today.KD foundation web site and KD "infocube" which is a puzzle cube made into first health education cube gives all necessary information for the parents, and given enormous benefit for the awareness and treatment of KD in India.

Etiology

Etiology remains unclear. Possible infectious agents or other non-infectious triggering agents may trigger immune complex vasculitis behind KD. Super antigen from infectious agents such as beta haemolytic streptococci also can trigger the immune complex vasculitis, evidenced by very high titre of ASO with signs and symptoms of KD fulfilling the criteria. At the same time, not all scarlet fever cases trigger IC vasculiitis.

Table 1: Susceptibility genes for Kawasaki disease recently reported.

Gene	Methods
ITPKC	Linkage analysis
CASP3	Linkage analysis
BLK	GWAS
CD40	GWAS
FCGR2A	GWAS
TGFB2, TGBR2, SMAD3	Association Study
HLA	GWAS

BLK: B lymphoid kinase; CASP3; Caspase3; HLA: HUMAN leucocyte antigen; ITPKS: Inositol tri phos Kinase; TGF: Transforming Growth Factor; FCGR2A: low-affinity immunoglobulin gamma Fc region receptor II-a.

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Table 2: Diagnostic Guidelines of Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome) Adapted from Kawasaki Disease Study Group of the Ministry of Health, Labour and Welfare Japan. Guidelines for the Diagnosis.

The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.	
S.No	**A. Principal symptoms**
1	Fever persisting for 5 days or more (inclusive of those cases in whom the fever has subsided before the 5th day in response to therapy)
2	Bilateral conjunctival congestion
3	Changes of lips and oral cavity: Redding of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
4	Polymorphous exanthema
5	Changes of peripheral extremities: (Acute phase): Redding of palms and soles, indurative edema (Convalescent phase): Membranous desquamation from fingertips
6	Acute nonpurulent cervical lymphadenopathy At least five items of 1~6 should be satisfied for diagnosis of Kawasaki disease. However, patients with four items of • recognized by Two-Dimensional (2D) echocardiography or coronary angiography recognized by Two-Dimensional (2D) echocardiography or coronary angiography symptoms can be diagnosed as Kawasaki disease when coronary aneurysm or dilatation is recognized by Two-Dimensional (2D) echocardiography or coronary angiography
	B. Other significant symptoms or findings
	The following symptoms and findings should be considered in the clinical evaluation of suspected patients.
1	Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage QRS complexes, effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (e.g., axillary), angina pectoris or myocardial infarction ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly), 2D echo findings (pericardial
2	Gastrointestinal (GI) tract: Diarrhea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
3	Blood: Leukocytosis with shift to the left, thrombocytosis, increased Erythrocyte Sedimentation Rate (ESR), positive C Reactive Protein (CRP), hypoalbuminemia, increased α2-globulin, slight decrease in erythrocyte and hemoglobin levels
4	Urine: Proteinuria, increase of leukocytes in urine sediment
5	Skin: Redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the finger nails
6	Respiratory: Cough, rhinorrhea, abnormal shadow on chest X-ray
7	Joint: Pain, swelling
8	Neurological: Cerebrospinal fluid (CSF) pleocytosis, convulsion, unconsciousness, facial palsy, paralysis of the extremities.

Table 3: Important clues and some differences were noticed in the clinical presentation of KD in India (observed by Dr. Jane C Burns).

Higher proportion of patients are older patients (>5 years). In US & Japan, less than 5-years age group.
Early Peeling in the acute phase of fever often within 10 days as opposed to desquamation occurring after 10-14 days in Japan and US
Thrombocytosis more frequently occur in Indian children
Peeling and thrombocytosis can establish diagnosis of KD in India.

Dengue fever triggering KD

Later in the course of Dengue fever, some of them have findings consistent with Kawasaki disease and Incidence of KD after dengue fever in India, notably significant. High dengue virus load modulates human microvascular endothelial barrier function and disrupts the function of inter endothelial junctional proteins during early infection with organ specific cytogenic production. Plasma leakage is the main pathophysiological feature in severe dengue, resulting from altered vascular barrier function associated with an inappropriate immune response triggered upon infection. High levels of cytokines, chemokine and adhesion molecules were differentially produced in a modelling study [15]. A total of 65 cases were diagnosed with KD during the period of 4-years and of the 48 who had a complete dengue serologic study, 18.7% of patients had proven dengue infection from a positive serologic study [16]. Dengue viral infection also induces cell proliferation and morphological changes of human endothelial cells. Potentially it can cause arteritis, including coronary arteritis, which is the hallmark of KD [17]. Fever persisting after Dengue fever due to IC mediated reactions leading to macrophage activation. Immune complexes were detected and quantitated in serum hepatitis, systemic lupus erythematous, subacute sclerosing panencephalitis, dengue haemorrhagic fever and other immune disorders.These dengue vectors may potentially and possibly carry the causative agent of KD [18].

Adeno virus can also trigger KD. In a monozygotic twin, boys had Adeno virus type 3 infection and subsequently developed KD proved by lab investigation specific to adenovirus [19].

Efforts to isolate the causative agents of KD, researchers focused on the microbiology of aerosols. Studies by Dr. Jane C Burns' et.al on environmental trigger had opened up new light on causative agents and results suggest that the environmental trigger for KD could be wind-borne. By enlarge a specific etiologic agent couldn't identify the causative agent for KD and considered as unknown to date [20]. These all-case reports and circulating IC isolation from the sera of KD suggest that KD is an immune complex vasculitis and further evidenced by the swine animal model in which similar manifestations reproduced by the horse serum [11,12].Hence, researchers can think how to mitigate IC in KD.

Genetic susceptibility

Analyses of genetic susceptibility to Kawasaki disease are contributing to the development of new treatments for Kawasaki

disease. Macrophages and neutrophils that are activated by various inflammatory cytokines mediated by IL-17 that is produced by T-helper cells (Th17) involve in the vasculitis. Recent advanced studies on gene analysis in KD were reviewed by Kei Takahashi and team (Table 1), contributing not only to prediction of disease susceptibility but also to improving our understanding of the pathogenesis of Kawasaki disease and development of new improved therapies. In addition, Th17/Treg imbalance may be an important factor causing disturbed immunological function. IL-17 induced by Th17 cells have proinflammatory properties and act on inflammatory cells, thereby inducing expression of cytokines and chemokines and resulting in tissue inflammation [5,21].

Histo pathology

Coronary arteritis begins 6-8 days after the onset of KD sometimes even earlier leads to inflammation of all layers of artery, begins as edematous dissociation of tunica media and infiltration of monocytes and lymphocytes. However, many neutrophils also were seen. Periarteritis further damage elastic lamina, SMC, leading to intense damage and dilate the artery. Inflammatory infiltration continues until 25th day of KD, then gradually decrease in number. Most often, we may not give much attention towards KD myocarditis [22]. Myocarditis is a well-recognized component of Kawasaki disease, with left ventricular dysfunction occurring in more than half of the patients during the acute phase of the disease, and may be transient. In KD, myocarditis develops even earlier than Epicardial coronary arteritis; it peaks by disease day 10 and then disappears gradually after day 20. Inflammatory cell infiltration, consisting mainly of lobulated leucocytes and large mononuclear cells, was seen in the myocardial interstitium in all cases [23]. It is well known that TNF-alpha is a key inflammatory cytokine that is initially produced by T lymphocytes, followed by a secondary TNF-alpha release from monocytes/ macrophages. TNF-alpha mediates endothelial cell activation through increased expression of adhesion molecules and upregulates expression of chemokines that are important in the orchestration of leukocyte-endothelial cell interactions. Hence, role of Infliximab in treating KD is important.

Animal Models

Various studies on animal models on vasculitis induced by candida albicans cell wall, lactobacillus casei, and serum albumin from horse serum in murine and swine models, mimicking almost all features of Kawasaki disease consistent with immune complex vasculitis may be involved in pathogenesis. Many publications had been proved that isolated circulating immune complex in the sera of Kawasaki disease, which was mainly done by Raji cell radioimmunoassay. Recent publication on rabbit model of arteritis displayed histopathological and ultrastructural features similar to those of KD [11,12]. Weanling rabbits and swine model may serve as experimental model for IC vasculitis that mimics KD than murine model. Therefore, circulating immune complexes, triggered by infectious agents implicating that immunopathologic mechanisms might be involved in the pathogenesis of vasculitis in KD [5-8].

Clinical signs and symptoms

Kawasaki disease is diagnosed based on characteristic clinical signs and symptoms. The principal symptoms of Kawasaki disease are a fever persisting for 5 days or longer, bilateral conjunctival injection, changes in the lips and oral cavity, polymorphous exanthema, changes in the peripheral extremities and acute non-purulent cervical lymphadenopathy. At least five of those principal signs and symptoms should be present for a diagnosis of Kawasaki disease [24,25]. Erethema around the BCG scar, perianal excoriation, 'Beaus line' on nail bed etc. will be additional supporting evidence for the confirmation of KD. IVIG resistance to initial IVIG dose is around 15-20%. Asymptomatic pyuria may be associated with co incidence of severe coronary artery lesion, so that we must overlook for the urinary pus cells as add on confirmatory diagnosis of KD for the early treatment. Diagnostic Guidelines of Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome) Adapted from Kawasaki Disease Study Group of the Ministry of Health, Labour and Welfare Japan (Table 2) [24]. Only deference in AHA criteria is Fever is superlatively considered as principal symptom and other 5 criteria was included as principal clinical findings. Either you can follow one of the criteria. But our foundation also considering fever is essential to diagnose KD.

KD can present with rare association as follows [26-29]

- Kawasaki patient rarely present with hypotension so called Kawasaki shock syndrome. And hyponatremia is a presenting symptom. Hence checking for electrolyte during acute phase is justifiable.

- Rarely papillary edema can develop. Hence Fundus exam also necessary to r/o papilledema.

- Bullae lesions, Gangrene, jaundice, interstitial nephritis, cystic fibrosis, varicella infection, autoimmune haemolytic anemia etc.

- Kawasaki Disease Presenting as Acute Intestinal Obstruction.

- Kawasaki Disease Complicated With Macrophage Activation Syndrome;Macrophage Activation Syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis, is a rare and potentially fatal complication of Kawasaki disease (KD). The persistence of fever with splenomegaly, hyperferritinemia, thrombocytopenia, and elevated Aspartate Aminotransferase (AST) should prompt the consideration of MAS complicating KD.

- Kawasaki disease and hepatobiliary involvement: report of two cases.

- Adult-onset Kawasaki disease (mucocutaneous lymph node syndrome) and concurrent Coxsackievirus A4 infection.

- Behcet's disease followed by Kawasaki disease. Behcet's disease is a rare systemic vasculitis of unknown origin HLA-B51 allele located on chromosome 6p has been the most strongly associated risk factor for Behcet's disease. (Unpublished clinical data reported to KD foundation)

- Kawasaki disease presenting with hemorrhagic pleural effusion.

- Meningococcal group a sepsis associated with rare manifestations and complicated by Kawasaki-like disease.

Table 4: Laboratory Investigations.

Hemoglobin
Total And Deferential Count (TC, DC), Platelet To Be Repeated Every 2-3 Days To See The Rising Count For Confirmation on KD
ESR, CRP, ASO, Sodium, Potassium
Liver Function Test; Bilirubin, Albumin, SGPT, SGOT
NS1 Antigen and Dengue IgM, IgG Serology, If Fever Persist for > 5days And Profound Thrombocytopenia Detects
Serum Ferritin
Urine Routine
Non Invasive Tests; Ultra Sound Abdomen, ECG, Echocardiogram (5-7Days)

Table 5: Second Line Therapy In Resistant Kawasaki Disease.

(A proposed protocol for resistant KD from the KD Foundation of India)	
Second Dose Of IVIG	1Gram /KG/BWT+ Intra Venous Methyl Prednisolone (IVMP) 30MG/KG/BWT OVER 2-3 HRS X 3DAYS. Then Followed by Oral 2-4wks
OR Infliximab	5MG/KG/BWT /Dose Infusion + IVMP
OR Etnarcept	0.8MG/KG/BWT /SC/WK + IVMP
OR ULINASTATIN	20000 -30000 UNIT/KG/ BWT OD IV X 3DAYS + IVMP
Cyclosporin-A	3-8MG/KG/Day PO X 5-6 Days Depends on a Febrile Period (Keep serum level 400-500NG/ML).
Plasma Exchange and Methotrexate/May be the Final Choice for Refractory KD	

Diagnostic serum biomarkers for Kawasaki disease

Current evidence suggests that NT-pro-BNP may be used as a diagnostic tool for KD. NT-proBNP has high diagnostic value for identifying KD in patients with protracted undifferentiated febrile illness.Positive results with ECG changes suggested that early evidence of KD myocarditis. Leucine-rich alpha-2-glycoprotein, LRG1 could be used as biomarkers to facilitate KD diagnosis based on clinical features [30]. Role of platelet and its regulating factors such as megakaryocytes, thrombopoietinand transforming growth factor beta1 has been studied in immune complex vasculitis in rabbit, found that significant rise of platelet and its regulating factors in immune vasculitis indicated their role in the pathogenesis of KD, and may serve as markers for the assessment of severity in KD. Thrombocytosis and periungual peeling an additional clue to diagnosis of KD in the absence ofother symptoms.

Adopted DNA-microarray technology to analyse gene expression profiles in patients with KD demonstrated that neutrophils in acute KD patients were not only expanded in number but also activated through the expression of a variety of late-stage granulocyte-specific genes such as Polycythemia Rubra Vera 1 (PRV-1) and haptoglobin compared with febrile controls. In accordance with these findings, serum granulocyte colony-stimulating factor (G-CSF) levels were also higher in IVIG-resistant patients than those in responsive patients. These results might indicate evidences for dysregulated immunological pathways in KD patients and provide possible tools for diagnosis and prognostics of KD. We also found that high-dose IgG specifically and completely inhibited accelerated expression of KD-related cytokines such as G-CSF, IL-6 and IL-1β by HCAEC in response to TNF-α. The suppression of these cytokine genes correlated closely with functional inhibition of a transcription factor, C/EBP-δ. These findings suggest that the clinical effects of IVIG on KD patients are at least in part due to its direct anti-inflammatory effects on the coronary endothelium in KD (Table 3)[31,32].

A study was conducted to explore the pathophysiological role of cell adhesion molecules (P-selectin and E-selectin) on the endothelial lesions in KD, and to look for the evidence of direct relationship between the plasma levels of soluble cell adhesion molecules (P- and E-selectin) and the incidence of the CAL. The increase of plasma PS and ES levels in KD acute phase and subacute phase might play an important role in the pathophysiology of the endothelial damage. E- and P-selectin may potentially be a predictor of CAL in patients with KD [33]. In addition to the routine laboratory investigations suggested, few special tests also can be performed to confirm the diagnosis of KD from other systemic illness (Table 4).

Giant aneurysm

Coronary giant aneurysm>8mm or ≥ 10 z score unlikely to resolve and need long term anticoagulant,keeping INR 2.2 and / or thrombolytic therapy.All such cases must be monitored every 4-6 months with ECG, Echo and TMT [34]. Severe long term complications can occur such as coronary artery stenosis resulting ischemic heart disease. Smooth muscle cells can migrate into intima producing myo-intimal proliferation; large amount of extracellular matrix and fibrosis results in calcification. Long-term follow up Studies done by Kato et al showed calcification 12% at 5y, 44% at 10y, and 94% at 20 y after diagnosis of KD.

Non-Giant coronary aneurysm

Most CAA from KD is small to medium sized. Regression can occur 50-60% within 1-2 years. Factors associated with regression are less that 1 year of age. Fusiform aneurysm gets resolve faster than saccular one. Smaller one and distal CA Involvement will have faster regression. Regression of aneurysm is usually by intimal proliferation.

Accelerated atherosclerosis

Persistent abnormal vascular wall morphology and dysfunction due to SMC proliferation and fibrosis of coronary walls may predispose early atherosclerosis. A 10-year FU study IVU Showed various degrees of intimal thickening at the site of regression.Endothelial dysfunction was proved in the form of increased constriction with

Table 6: Scoring Systems.

Kobayashi score 1. (≥5 points; sensitivity 76%, specificity 80%)		
Na	≤133mmol/L	2
AST	≥100IU/L	2
Day of starting treatment (or diagnosis) Day 4 after onset or earlier		2
Neutrophils	≥80%	2
CRP	≥10mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤12 months	1
Egami score(≥3 points; sensitivity 76%, specificity 80%)		
ALT	≥80 IU/L	2
Day of starting treatment (or diagnosis) Day 4 after onset or earlier		1
CRP	≥8mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤6 months	1
Sano score(≥2 points; sensitivity 77%, specificity 86%)		
AST	≥200IU/L	1
Total bilirubin	≥0.9mg/D	1
CRP	≥7mg/dL	1

acetylcholine and poor dilatation with isosorbide dinitrite. Transient dilatation didn't show any long-term ischemic findings.

Management issues

Recent review on pathogenesis again prompts us to investigate new drugs in KD. TNF-α is a pleiotropic inflammatory cytokine that has been strongly implicated in the development of aneurysm formation in patients with KD. Infliximab and Etanercept are examples of these TNF-α receptor antagonist. Etanercept, although a TNF-α antagonist, has different mechanisms to infliximab. Infliximab is a chimeric monoclonal immunoglobumin-G (IgG) antibody that targets transmembrane TNF-α. This damages the cells, which express TNF-α, including cardiomyocytes [35,36]. On the other hand, etanercept is a soluble fusion protein receptor that works more broadly on TNF (both TNF-α and lymphotoxin), and binds to only circulating TNF-α, thereby avoiding the adverse effect seen in infliximab. But we need more studies and both drugs plays important role as a pharmacological agent in recrudescent fever after first dose of IVIG or as a first line therapy. Markedly activated neutrophils or high plasma neutrophil elastase in-patient with KD have been implicated in poor response to IVIG. Ulinastatin is a urinary tripsin inhibitor and has a property to inhibit neutrophil elastase. Treated with Ulinastatin as Initial treatment for KD, resulted in lower incidence of CAL in which 3% as opposed to 7% in control group. Methotrexate is a folic acid antagonist suppresses lymphocyte proliferation and has role in modulating cytokines especially IL-6 highly expressed in KD. INOSITOL TRIPHOSHATE 3-KINASE Cact as a negative regulator of T-cell activation and activated T cells may play a pivotal rolein pathogenesis of KD. Cyclosporin will suppress the activity of T cell.

Studies have demonstrated the pivotal role of Tumour Necrosis Factor (TNF)-a-mediated matrix metalloproteinase (MMP)-9 activity, in modulating key pathogenic stages of disease leading to coronary artery damage and in the pathogenesis of elastin breakdown in a murine model of KD, Lactobacillus casei cell wall extract-induced coronary arteritis. Doxycycline inhibits T cell activation and TNF-a production in peripheral immune cell and inhibits directly MMP-9 enzymatic activity derived from TNF-a-stimulated vascular smooth muscle cells. Therefore, doxycycline can mitigate TNF-a-induced MMP-9-mediated coronary elastin breakdown and improve coronary outcome. Antioxidants such as high dose of vitamin ACE has a greater role in mitigating coronary artery lesion as an add on drug therapy. Additional IVIG shows 71% response & 30% resistance. In such cases, Steroid pulse therapy (Methyl Prednisolone) to resistant IVIG cases may give 100% response. Personally, I feel that in all cases of IVIG resistant group, we should start multiple or in combo drug therapy in which steroid pulse therapy could be essential to prevent or further damage of coronary arteries [37].

Resistant KD

Additional IVIG shows 71% response & 30% resistance. In such cases, Steroid pulse therapy (Methyl Prednisolone) to resistant IVIG cases may give 100% response. Personally, I feel that in all cases of IVIG resistant group, we should start combination drug therapy in which steroid pulse therapy could be essential to prevent or further damage of coronary arteries. Management protocol for IVIG resistant group is given in Table 5 as per the personal experiences and may vary from person to person. Plasma exchange may be considered as another mode of treatment if you have facility for plasmapheresis under an experienced hematologist to remove circulating immune complexes, thus we can save the cost of IVIG in developing countries and age also matter. Younger children cannot undergo plasmapheresis due to various procedural reasons. Different scoring systems were developed by various authors as per their experiences (Table 6).

Long-Term Management of Kawasaki Disease: Implications for the Adult Patient

Many scoring systems are available to predict Unresponsiveness to IVIG therapy

Threshold Point: Current long-term management protocols are calibrated to the degree of maximal and current coronary artery involvement reflecting the known likelihood of severe long-term cardiac complications. It has recently been suggested that all KD patients may be at potential risk of severe long-term cardiac complications. Based on the available evidence, patients with multiple large and/or giant CAA are at substantial risk of severe long-term cardiac complications and should have regular specialized follow-up. Patients with transient or no CAA has not been reported to be at risk of severe long-term cardiac complications. The influence of KD on the atherosclerotic process remains sub-optimally defined, and should be the focus of future studies. It is generally accepted that patients with no or transient coronary artery dilation during acute KD, comprising 95% of individuals diagnosed with KD in the past 25 years, live with long-term cardiovascular health comparable to the general population. An intermediate group of patients, those with small to medium sized CAA that may or may not have regressed, have an unclear long-term prognosis and, hence, may receive suboptimal follow-up include TMT and ECG every 1-2 years.

Crystal et al found coronary artery z-score regression in

patients with normal acute-phase coronary arteries, suggesting that dilation is a common and spontaneously resolving characteristic of acute illness. As such, dilation is an acute-phase phenomenon of endothelial dysfunction and coronary artery deregulation, resulting in no permanent changes to the vasculature. However, endothelial dysfunction may persist in some patients with aneurysmal coronary artery dilatation [38,39].

Long-term fate and complications of giant CAA

Although rare, giant CAA (8mm or Z score 10) are highly unlikely to resolve. They are associated with the most severe long-term complications, including progression to stenosis or occlusion, resulting in ischemic heart disease. Stenosis of persistent and regressed CAA may occur as a result of myointimal proliferation, an intrinsic process of post-acute KD, in which smooth muscle cells migrate from the media to the intima, producing large amounts of extracellular matrix and fibrosis. This process may further result in calcification of the aneurysm site by a mechanism similar to arteriosclerosis, which may be accelerated with persistent inflammation in some patients .Calcification occurs primarily at the media-intimal or the sub endothelial surface. Calcification is a prevalent and unique characteristic of giant CAA; affecting 12% at 5 years, 44% at 10 years, and 94% at 20 years after diagnosis [36,37]. Thrombotic occlusion may also progress to calcification after the organization and recanalization of a non-occlusive mural thrombus. Myocardial infarction is the major cause of death from KD, resulting either from sudden thrombotic occlusion of a vessel, or from gradual stenotic occlusion [40].

Optimal definition of CAA to be small if the z score is > or = 2.5 to < 5.0, large if the z-score is > or = 5.0 to < 10.0, and giant if the z score is > or = 10.0. This classification seems to appropriately apply to the circumflex branch despite a lack of normal values for this branch. The current AHA classification might not accurately classify CAAs in KD patients. Accurate classification is important for defining management and prognosis consistently across patient age and size. Based on studies reviewed in this meta-analysis, and the significant benefit in terms of reduced myocardial infarction and death, long-term oral anti-coagulation with warfarin together with aspirin appears to be the current best management of children with giant coronary arteries [41,42].

Conclusions

Kawasaki disease is a systemic vasculitis of unknown origin, but confirmed as an immune complex vasculitis triggered by virus, bacteria, fungus, dust mite etc. KD should be kept in mind as one of the possibilities in a case of dengue if fever persists beyond the expected duration. Gold standard therapy for acute phase of KD is IVIG and aspirin, but add on therapy will certainly decrease the incidence of coronary vasculitis. In resistant cases, foundation recommends combination of steroid therapy. Giant aneurysm never will resolve and need timely follow up and appropriate care and management.

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