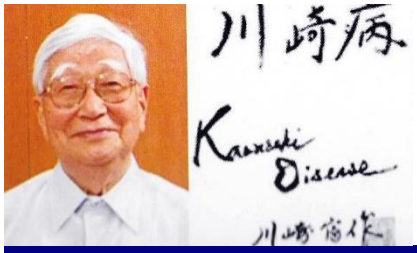

Kawasaki Disease

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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 presenting pattern in 50 cases had been published 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 in children (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 our understanding of pathogenesis and newer modalities in management of KD.

Epidemiology

KD is more prevalent in Asian children. According to recent epidemiologic studies, Asian populations have a much higher incidence of KD (13). Seasonal variations, chronological and geographic clustering have been observed. Approximately 80-90% of patients with KD are seen below 5 years of age. **Japan** has the highest annual incidence in the world (308 per 100,000 children < 5 years of age between 2013-2014 and increased further to 330.2 in 2015,

followed by **South Korea** 199.7 per 100 000 children < 5 years of age in 2014, and **Taiwan** has the third highest 82.8 per 100 000 children <5 years of age in 2010. In Taiwan,they estimate that approximately 700 KD patients in a year are newly diagnosed. In **Hawaii**, with its complex multi-racial and multi-ethnic population overall annual incidence is about 50.4/100,000; for Japanese ethnic children in Hawaii, the rate is 210. **Beijing** has reported an increased incidence, increasing from 40.9 to 55.1 in 2004, increased to 110 (2014) per 100 000 persons. In **Shanghai** it increased from 16.2 (1997) to 71.9 (2012) per 100000 children <5 years (13-17).In **Hong Kong**, the average annual incidence was 39 per 100 000 between 1994 and 2000. 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. Coronary artery lesions after 30 days of illness showed only 3% in Japan. Decreasing trend of coronary artery complications in Japan may be indicated that almost all KD cases had received IVIG as first line of therapy. The ratio of male and female KD patients approximates 1.5:1 in virtually all countries.

KD has striking age distribution, with almost 100% cases occurring in children, 80-90% in children <5years and 50% in those <2 years old. We must admit seriously that we do not have sufficient data to present the epidemiology in India till today except regional data from the individual medical colleges. KD incidence at **Chandigarh, North India** during 2009-2014 was 7/100,000 children below 15 years of age. First case was diagnosed in 1994. The number of cases detected during 1994-2017 is 680 and tend showed two-fold rise of KD cases for last four years (2014-2017). Recurrent KD was 0.98% and 2% was within 10 months of first episode. Incomplete KD was more common during recurrence. (18) The recurrence rate is approximately 2% in Taiwan and 3.5% in Japan. The case fatality rate is <0.1% in both **Japan and Taiwan**.The peak seasons of KD are late spring and summer in

Taiwan.(19)The web sites for KD foundation, KD society of India, mobile android appand KD “infocube” ; a puzzle cube made into first health education cube made from the foundation gives all necessary information for the parents, and given enormous benefit for the awareness and treatment of KD in India.

Etiopathogenesis

Etiology still remains unclear. Both epidemiological and clinical features of KD strongly suggest possible infectious agents. Other non-infectious triggering agents also may trigger immune complex vasculitis leading to signs and symptoms manifested in KD. Superantigen is an unconventional protein leads to massive T cell activation leads to cytokines production, Anti body against endothelial cell ligands which may be an antigen of viral orbacterial? Super antigen from infectious agents such as beta haemolytic streptococci can trigger the immune complex vasculitis, evidenced by signs and symptoms with criteria favour for KD especially coronaries are involved with very high titre of ASO. Staphylococcal or streptococcal are suspected to produce superantigen.At the same time not all scarlet fever cases trigger IC vasculitis.Some of the implicated pathogens are staphylococcus, streptococcus, Yersina, Adenovirus, human parvovirus and herpesvirus etc. The failure of KD patients to antibiotic therapy makes a viral etiology more likely than bacterial. Moreover, the prevalence of CD 8 T cells in the inflammatory infiltrate and the upregulation of cytotoxic T cell and interferon pathway genes in the coronaries of children who have died of KD are very suggestive of a viral etiology. Rowley and Shulman proposed possible model pathogenesis as unknown infectious agents possibly viral agent infects ciliated bronchial epithelium cells in a small subset of genetically predisposed children. Agents enter blood stream via macrophages and antigen in circulation will attach B cell and mediated plasma cell and will generate antibody. This will form antigen antibody circulating immune complexes

damages endothelium of medium and small vessels particularly coronary artery with further neutrophil mediated lysosomal enzymes, and platelet aggregation damages and causing aneurysm of vessel wall. (17)

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, chemokines and adhesion molecules were differentially produced in a modelling study. (20)**.** 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.(21) 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. (22) 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 (23).

Adeno virus can also trigger KD. In a monozygotic twin boy had Adeno virus type 3 infection and subsequently developed KD proved by lab investigation specific to adenovirus (24).

Efforts to isolate the causative agents of KD, researchers focused on the microbiology of aerosols. Studies by 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 (25). By enlarge a specific etiologic agent couldn't identify the causative agent for KD and considered as unknown to date (24). 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)

Genetic susceptibility

Analyses of genetic susceptibility to Kawasaki disease are contributing to the development of new treatments for Kawasaki disease. Macrophages and neutrophils which 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, 26).

Table 1. Susceptibility genes for Kawasaki disease recently reported

Gene	Methods
ITPKC	Linkage analysis
CASP3	Linkage analysis
BLK	GWAS
CD40	GWAS
FCGR2A	GWAS
TGFB2, TGFBR2, 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.

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 till 25th day of KD, then gradually decrease in number.Most often we may not give much attention towards KD myocarditis (25). 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 (27,28). 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 also 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 in Research

Various studies on animal models on vasculitis induced by candida albicans cell wall, lactobacillus casei, 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 thatmimics KD than murine model. Therefore, circulating immune complexes, triggered by infectious agentsimplicating that immunopathologic mechanisms might be involved in the pathogenesis of vasculitis in KD (5 – 8). Changes in the coronary arteries after immune complex vasculitis were studied (Table 2& Fig.1A-D). Histopathology in human KD coronary arteritis is very much similar to immune- complex vasculitis induced by horse serum.

Table 2 . Histopathology of coronary artery in immune complex vasculitis

02-04 days	**Leucocytic and lymphocytic cellular infiltrates in the myocardium, perivenular and peri-arterial infiltrates inthe heart. Cellular infiltrates in the smooth muscle cells and**

around the vasovasorum of the aorta and in the distal tubular areas of the kidney. No significant changes in other vessels and organs.

05-13days

Intimal thickening, inner smooth muscle cells proliferation (Fig.1 A-B), patchy edematous changes and early SMC disorganization in coronary arteries. Cellular infiltrates were few. Iliac artery showed mild intmal thickening. No significant changes in other vessels and organs

14-24 days

Intima and inner SMC proliferations, moderate to severe disorientation of SMC (Fig.1C), edematous separationof SMC (Moth eaten appearance), Subintimalchanges, such as coagulation of the cytoplasm, and disorientation, separation, cytolysis, vacuolization, degranulation, collagen deposition in coronaryarteries. Intimal proliferation of intramural artery. No significant changes in other vessels and organs.

25-60days

Patchy areas of fibrosis within the SMC (Fig. 1D), resolving stages, No further progression of proliferation of SMC in the tunica media and intima. No significantchanges in other vessels and organs.

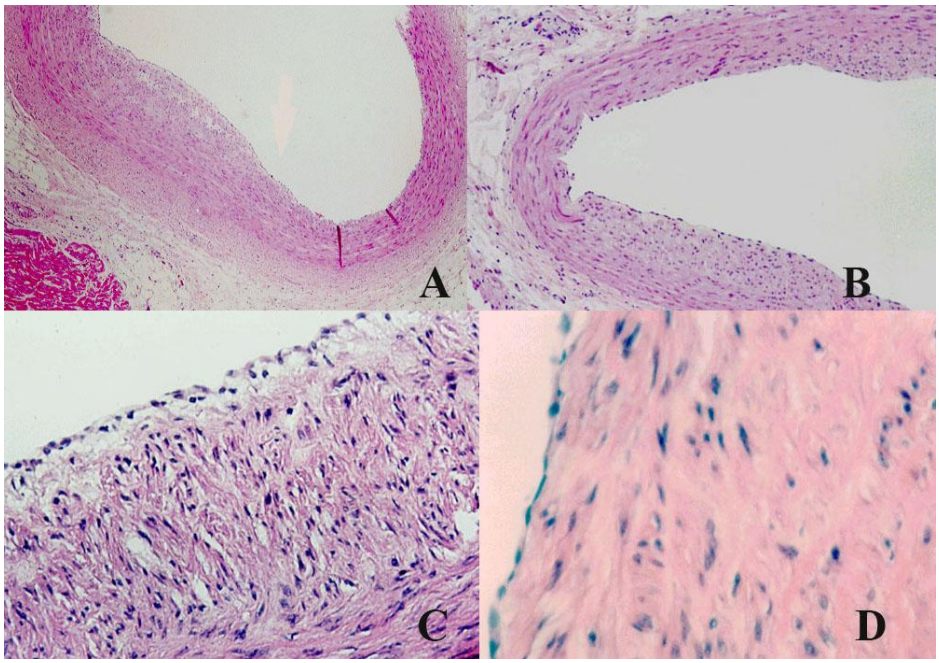

Figure 1 A-D: A-B; Left anterior coronary artery showed intimal proliferation extending to media (5-13days), C; Disorientation of smooth muscles in vertical direction (14-24 days), D; fibrosis of the arterial wall (25-60days)

Clinical signs and symptoms

Kawasaki disease is diagnosed on the basis of characteristic clinical signs and symptoms. The principal symptoms of Kawasaki disease are a **fever persisting for 5 days or longer, bilateral conjunctival injection without exudate, changes in the lips and oral cavity, polymorphous exanthema, changes in the peripheral extremities and acute non purulent cervical lymphadenopathy (>1.5cm, usually unilateral, even >1cm in infant is significant).** At least five of those principal signs and symptoms should be present for a diagnosis of Kawasaki disease. (29, 30). 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 3).** (29) **High irritability and persisting fever** in a child especially in less than 6 months of age, **Erythema around the BCG scar** (18-24%), **perianal excoriation, 'Beaus line' on nail bed** etc. will be additional supporting evidence for the confirmation of KD.KD eastern and northern India cohort had found that **orange brown chromonychia** is a novel finding seen in 63% of patients. and IVIG resistance to initial IVIG dose is around 15-25% as per the unpublished datas from deferent countries. **Asymptomatic pyuria may be associated with co incidence of severe coronary artery lesion, so that we must overlook for the urinary pus cells and thrombocytosis or rising trend of platelet count may consideras an add on confirmatory diagnosis of KD.** 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 society also considering fever

isessential for the diagnosis of KD. Majority were complete KD up to 84% and rest are incomplete KD.**Few important diagnostic clues are irritability, rising trend of platelet, early periungual peeling, erythema around the BCG scar, nonexudative clean bulbar conjunctivitis, chromonychia and beaus line, will lead to further confirmation**from other differential diagnosis overlapping with KD diagnosis (**Table 4, Figure 2 A-E**).All cases of suspected KD must evaluated for incomplete subset of KD and should be treated as KD once the criteria fulfilled for incomplete KD to prevent coronary artery complications, in fact incomplete KD may more prone for developing coronary artery complications than complete KD.**(Table 5)**Other important diseases overlapping with the signs and symptoms of KD should be scrutinised for differential diagnosis (**Table 6).**

Table 3. 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 (deference of JMC from American HeartAssociation KD criteria is fever is included in the principal symptoms, where as fever is essential to diagnose KD in AHA criteria)

The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

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): Reddening of palms and soles, indurative edema

(Convalescent phase): Membranous desquamation from fingertips

- **6. Acute nonpurulent cervical lymphadenopathy**
- At least five items of six should be satisfied for diagnosis of Kawasaki disease by JMC and five of six with fever should be satisfiedfor AHA criteria. Further one point less in JMC or 4/5 criteria considered as incomplete KD
- However, patients with four items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm or dilatation isrecognized 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, abnormalQ wave, low-voltage QRS complexes, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly)
- 2D echo findings (pericardialeffusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (e.g., axillary), angina pectoris or myocardial infarction
- 2. Gastrointestinal (GI) tract: Diarrhoea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase ofserum 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 haemoglobin 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, rhinorrhoea, 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 4. Few important striking signs in KD to confirm the diagnosis

• Irritability with fever
▪ Early peri ungual and perianal excoriationoften within 10 days in the acute phase of fever
▪ Rising trend in thrombocytosis more frequently occur.
▪ Erethema around the BCG scar
▪ Orange brown Chromonychia a novel finding seen in 63%
▪ Beaus line in 3rd to 4th week
▪ Clean bulbar conjuctivitis @ Thrombocytosis and peeling can establish diagnosis of KD in India

Table 5 ; evaluation of suspected incomplete Kawasaki disease

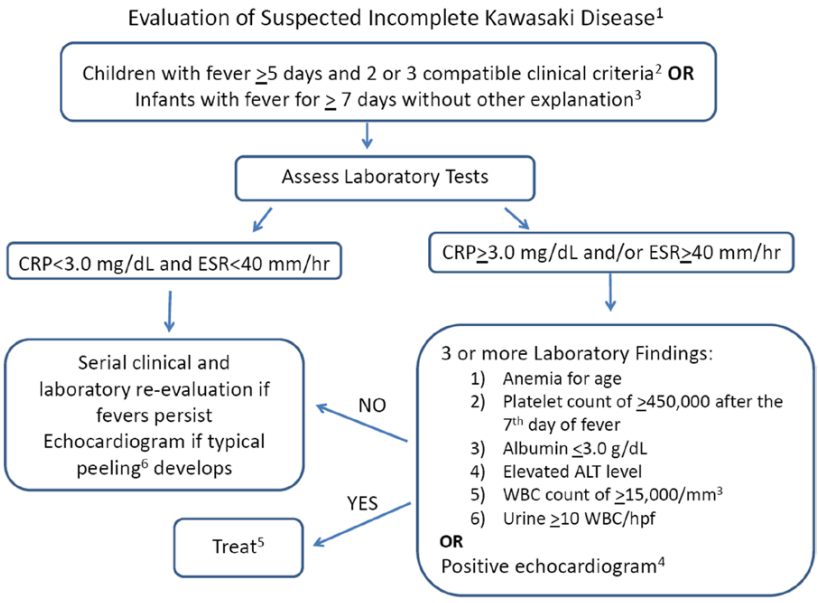

Table 6. Major Deferential Diagnosis

▪ **MEASELS**
▪ **SCARLET FEVER**

▪ **JUVENILE RHEUMATOID ARTHRITIS**
▪ **STEVENS-JOHNSON SYNDROME**
▪ **DRUG REACTIONS**
▪ **TOXIC SHOCK SYNDROME**
▪ **LEPTOSPIROSIS** ▪ **MERCURY POISONING**
▪ **STAPHYLOCOCCAL SCALDED SYNDROME**

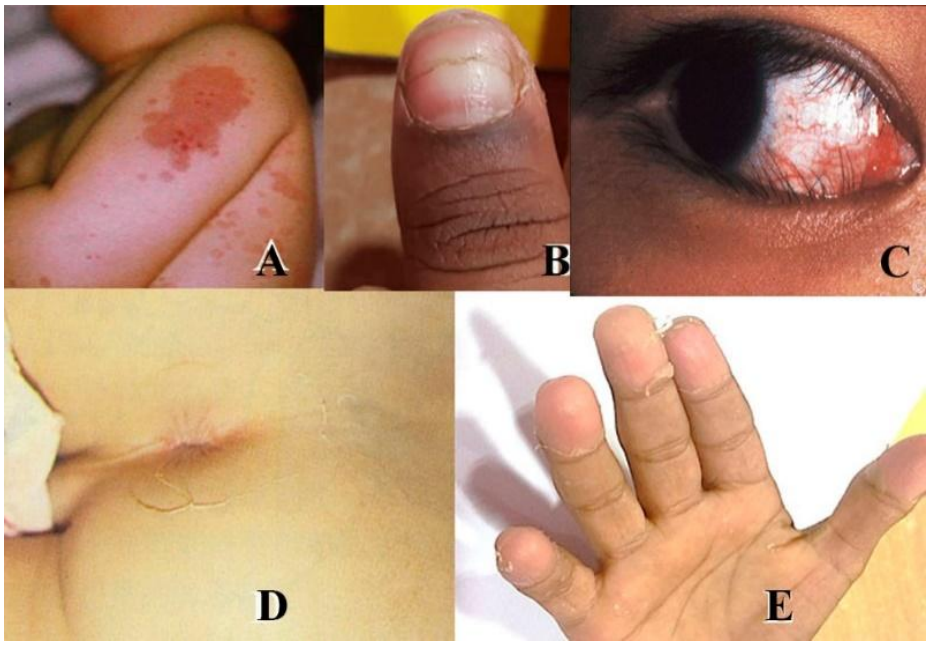

Figure 2 A-E; Erythema around the BCG scar, B; Beaus line- A transverse line or groove well seen over the thumb nail 3-4week, C; Non purulent conjunctivitis D; Perianal excoriation, E; Typical periungual desquamation

Cutaneous manifestation in Kawasaki disease

Kawasaki disease (KD) is the second common vasculitis in childhood following Henoch–Schönlein purpura. The commonest cutaneous manifestation is the rash which usually

appears by the 5th febrile day. It is usually **erythematous maculo-papular** (Fig.3A) present predominantly on the trunk. However, a variety of rashes have been described: **scarlatiniform, erythema multiforme like, erythroderma**; and can sometimes be pruritic. A vesico-bullous or pustular rash is not consistent with KD, but erythema nodosum, ulcerative or bullous lesion can rarely occur in association with KD. Affection of the oral mucous membrane leads to erythema, **dry fissured lips** and sometimes a **strawberry tongue**.

Extremity changes form one of the striking diagnostic features in KD. The erythema of the palms and soles together with edema of the hands and feet which may occasionally be painful often occur in the acute phase. The other classical finding is the periungual desquamation in the fingers and toes that starts around the end of 2nd week (**Figure 2E, Fig.3 B&E**). Though a consistent clinical finding, but because of the late appearance in the subacute phase its clinical utility lies in only confirming the diagnosis retrospectively. **The periungual desquamation (Figure 2E)** is however preceded by **perineal desquamation**(**Figure 2D**) that may be present as early as end of 1st week. Few patients may also have peri/ supra orbital erythema followed by excoriations. Another well described albeit a bit rare sign are the transverse grooves called Beau's lines**(Figure 2B**) on the nails which may appear as late as 1 to 2 months after the disease onset. **Beau's lines** are better felt than visually appreciated.

An interesting finding which is almost pathognomonic of KD is **reactivation of the BCG scar (Erythema around the scar may turn into ulcerative in some cases**(**Fig.3C**) observed in 10-15% children. A recently described clinical finding is **orange-brown chromonychia** which means an abnormal reddish/ orange brown change in colour of the nail plates and / or subungual tissue. The coloured lines start appearing usually around the 5th to 8th day of illness, though they may be noticed as early as the 4th day of fever mandating it as an early sign in the diagnosis. Once it appears the colouration stays unchanged over the next 7 to 10 days. Better appreciated in the fingers (Fig.3D) than the toes, they start disappearing by the

end of 2nd week. Thus, on appearing they are present throughout the acute phase of illness as opposed to most of the classical clinical signs in KD which are known for their markedly temporary appearance.

Other than the chromonychia, few case reports describe some inconsistent nail changes following KD like **onycholysis, onychomadesis** (spontaneous separation of the nail from the matrix), spontaneously resolving pincer nail deformity (transverse curling of the nail along its longitudinal axis) and **leukonychia partialis** (abnormally white proximal portion of the nail) . However, all these nail abnormalities are nonspecific, maybe associated with other systemic triggers and generally resolve spontaneously within 1–2 months.

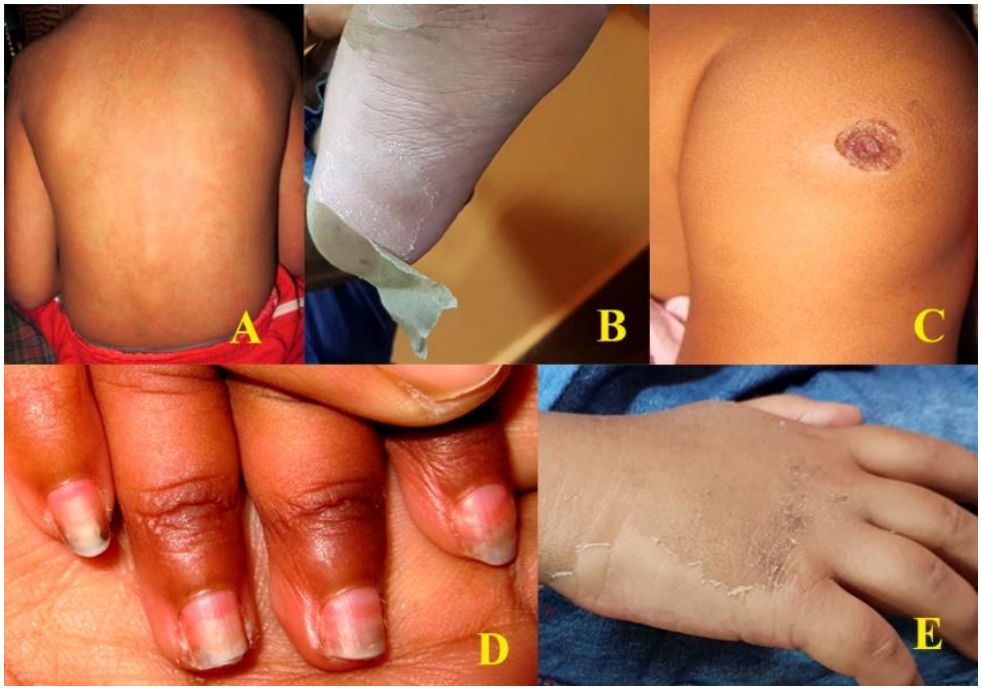

Fig.3 A-E; A: Erythematous maculo-papular rashes predominantly present on the trunk B: Exfoliation starts as periungual and then to entire sole and palm in severe cases C. Erethema around the BCG scar turning to mild ulcrerative changes. D: Chromonychia-Stricking brownish orange colour change of nails in acute phase. E: Exfoliation may extend to dorsum of hand in later phase

Myocarditis in Kawasaki Disease

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. (27, 28)Cardiac MRI is considered the Gold standard noninvasive test for diagnosing of Myocarditis. Augmented inflammatory condition can be revealed by increased intensity of T2 W images.Severity of detecting edema in myocardium in acute phase of Myocarditis is 84% with specificity of 75%. Multiple foci of Hyper-enhancement in the myocardium during early Gadolinium enhancement EGE, consistent with Myocarditis. Though MRI gives diagnostic confirmation, echo scan is sufficient to rule out myocarditis.Cardiovascular biomarkers for myocarditis in KD are CKMB, Cardiac troponin I (25-35% elevated in biopsy proved myocarditis). N-terminal pro-B-type Natriuretic peptide (NT-pro BNP) and soluble ST2 (sST2) were elevated in acute vs. convalescent KD. (35) When the titre of Pro BNP is over 450 pg/ml and the patient probably has an abnormal ECG, is most likely to have myocarditis. Echocardiographic features of myocarditis are pericardial effusion, left ventricular systolic dysfunction evidenced as low ejection fraction, mitral regurgitation. The overall sensitivity of echo in picking up CAL is 95%. Sensitivity will decrease when lesions ate the distal area, then we advise for CT angio.Important laboratory investigations to be performed to diagnose KD are given in **Table 7.**

Rare associationswith Kawasaki disease (30-34)

- 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, auto immune haemolytic anemia etc.
- Kawasaki Disease may presentas Acute Intestinal Obstruction.
- Kawasaki Disease complicated with Macrophage Activation Syndrome; Macrophage activation syndrome (MAS), also known as secondary hemophagocytic lympho-histiocytosis, 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 may associate with hepatobiliary involvement.
- Adult-onset Kawasaki disease (mucocutaneous lymph node syndrome) and concurrent Coxsackievirus A4 infection.
- Kawasaki disease followed by Behcet's 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. 5- Year old boy manifested signs and symptoms of KD with history of Bechcet's disease at 6months prior to KD. HLA-B51 may associate rarely with KD. (unpublished clinical data reported from a Canadian patient to KD foundation)
- Kawasaki disease may present with haemorrhagic pleural effusion.

- Meningococcal group A sepsis associated with rare manifestations and complicated by Kawasaki-like disease.
- Laboratory investigations to be done from the day of suspicion of KD till discharge is essential for the appropriate treatment, follow up and evaluation forthe treatment response.(Table 7)

TABLE 7. LABORATORY INVESTIGATIONS
Haemoglobin, Complete blood count
Platelet count to be repeated every 2-3 days to see the rising trend (Thrombocytosis)
ESR, CRP, ASO
Sodium, Potassium, Pro BNP
Liver function test; Bilirubin, Albumin, SGPT, SGOT,
NS1 antigen and dengue IgM, IgG serology, **if fever persist for > 5-days with profound Thrombocytopenia detects**
Serum Ferritin
Urine routine
Non invasive tests; Ultra sound abdomen, ECG
First Echocardiogram at 5-7days of acute stage or as soon as you diagnose KD as a baseline echo, **if first echo is normal repeat after 5 days**

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, (NT-pro BNP 1 Year >550PG/ML, 1-2Y >202PG.ML;2-3 Y>189Pg/ml; >3y 152PG/ML). NT-proBNP was significantly higher in KD LRG1 could be used as biomarkers to facilitate KD diagnosis based on clinical features. (35). Role of platelet and its regulating factors such as megakaryocytes, thrombopoietin and 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 of other 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 polycythaemia 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 (36, 37).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 (38).

CORONARY ANEURYSMS

The 2017 AHA guidelines emphasized the application of Z scores for coronary artery evaluation and classified the severity of coronary abnormalities by using Z scores. Coronary Z scores of +2.5, +5.0, and +10.0 were recommended as the cut-off points for small, medium-sized, and giant coronary aneurysms, respectively **(Table 8).** These Z scoring systems areusually applied for the pRCA, LMCA, and pLAD. Other coronary segments such as circumflex can be evaluated by comparing them to adjacent segments.(39)

Table 8 Coronary Z score classification and timing of echocardiography.

Severity of coronary artery abnormality	Z score or diameter	Timing of echocardiography
No involvement	Z score $< +2$	1- 2 weeks and 4–6 weeks after treatment
Dilatation only	Z score $\geqq +2$ to $< +2.5$, or Initial Z score $< +2$, decrement of Z score $\geqq +1$ during follow-up	1- 2 weeks and 4–6 weeks after treatment
Small aneurysm	Z score $\geqq +2.5$ to $< +5$	Twice per week till no progression
Medium aneurysm	Z score $\geqq +5$ to $< +10$ and absolute diameter < 8 mm	Twice per week till no progression
Large/Giant aneurysm	Z score $\geqq +10$ or absolute diameter $\geqq 8$ mm	Twice per week, at least once weekly in first 1.5 month, then monthly until the 3rd month

Giant Aneurysm

Giant aneurysm can occur in 1% of CAL andis defined as diameter >8mm or ≥ 10 z score by coronary artery measurement**(Fig 4)**. As per the echocardiographic follow up giant aneurysm will never resolve. In such cases long term antiplatelet and anticoagulant therapy is needed, by keeping INR 2.2. Further follow up is very essential and must be monitored every 4-6 months with ECG, Echo and TMT (39).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 10 y, 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 than1 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 IVUShowed various degrees of intimal thickening at the site of regression. Endothelial dysfunction was proved in the form of increased constriction with acetylcholine and poor dilatation with isosorbide dinitrate. Transient dilatation didn't show any long term ischemic findings. In children atherosclerosis may occur after 10-12 years only. Fat restricted diet should be advised in later adolescent and middle-aged life.

Management of Kawasaki disease

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 antagonists. Etanercept, although a TNF-α antagonist, has different mechanisms to infliximab. Infliximab is a chimeric monoclonal immunoglobulin -G (IgG) antibody that targets transmembrane TNF-α. This damages the cells which express TNF-α, including cardiomyocytes (40-42). 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 agents 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 C act as a negative regulator of T-cell activation and activated T cells may play a pivotal role in 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 also in the pathogenesis of elastin breakdown in a murine model of KD, Lactobacilluscasei cell wall extract-induced coronary arteritis. **Doxycycline** inhibits T cell activation and TNF-a production in peripheral immune cell and also 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 of vitamin A,C&E has a greater role in mitigating coronary artery lesion as an add on drug therapy. (42) Additional IVIG shows 71% response & 30% resistance. In such cases **Steroid pulse therapy (Methyl Prednisolone**) to resistant IVIG cases may give 100% response.**Treatment protocol with dosages of medications given in Table 9.**

Table 9; Treatment protocol of KD in acute phase

1. **IVIG2g/kg BW as single dose over a period of 24hrs (it can be given from the day of diagnosis usually after 5days of fever and evenup to 18days in cases of late diagnosis.But the evidences of high inflammatory markersmandatory.**
2. **Aspirin 60mg/kg /Body weight/dayin 6hrly with sucralfate or with antacids /ranitidine or other proton pump inhibitors as per your choice till child become afebrile for at least 48hrs.**

- **Aspirin treatment should be adjusted to a low dosage 3 to 5 mg /kg/day as single dose,once after the fever subsides for 48 to 72 hrs of IVIG infusion.**
- **If no Coronary artery lesions, Aspirin should continue till 6-8wks**
- **If coronary artery is involved, continue Aspirin till CAL resolves including intimal irregularities and thickening. For giant aneurysm Aspirin should continue Life term.**
- **With Coronary artery lesionexcluding simple ectasia, add clopidogrel 0.2 to 1mg/kg/day max 75mg/day till the resolution of CAL by your Echo follow up**

3. **With Giant aneurysm; Add warfarin (keep INR 2.2)/Coumadin/low molecular weight Heparin. LWMH is reasonable to administer in cases with Z SCORE >10**

- ***Infliximab may also be considered as first line of therapy when cases admitted with diagnosis of severe CAL and in anticipated IVIG resistant group. Infliximab will be more economical than IVIG*.**

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. Authors feel that we should start combination of drug therapies in in allIVIG resistant cases, in which steroid pulse therapy could be essential to prevent or further damage of coronary arteries(29,47). We don't want to see further risk in developing coronary aneurysms in recrudescent fever. Management protocol for IVIG resistant group is given in **Table 10** as per the personal experiences and may vary from person to person. CRP level of>8mg/dl after initial IVIG are likely to fail additional IVIG. 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 No.11**

KD Shock syndrome

The incidence of KD shock syndrome (KDSS) is estimatedto be ≈7%.118,119 KDSS can be defined as the presenceof hypotension and shock requiring the initiation ofvolumeexpanders, the infusion of vasoactive agents, ortransfer to intensive care units. Shock in KDSS is oftenmoderate, with low lactate values and the need for treatmentwith inotropic and vasopressor agents.Althoughhemodynamic instability generally improves quickly oncetherapy with diuretic agents and vasopressor agents isinitiated, a mild degree of

ventricular diastolic dysfunctioncan persist after acute management. The causesof KDSS may involve the release of endogenous moleculesthat mediate a decrease in peripheral vascular resistance,myocardial dysfunction from myocarditis withor without myocardial ischemia, and capillary leakage,but the exact underlying mechanisms remain unclear.KDSS is often associated with more severe laboratorymarkers of inflammation and higher risk of coronary arterialdilation.Such cases are also more likely tobe resistant to IVIG therapy and to require additional anti-inflammatory treatment.(29)

TABLE. 10FIRST LINE THERAPY IN RESISTANT KAWASAKI DISEASE (Modified from AHA)

Second dose of IVIG2 gram /kg/bwt	
IVIG + Prednisolone IVIG: 2 g/kg IV + Prednisolone 2 mg/kg/day, divided every 8 h until afebrile, then prednisone orally until CRP normalized, then taper over 2–3 wk	
IVMP	**Advised not with IVIG but can be tried sepataevely Intra venousmethyl prednisolone(IVMP) 30 mg/kg/ body weightover 2-3 hrs x 3days.Then followed by oral 2-4wks**
or Infliximab*5 mg/kg/bwtsingle infusion x 2hrs + IVMP	
or Etnarcept 0.8mg/kg/bwt/sc/wk +IVMP	
or Ulinastatin	**20000 -30000 unit/kg/ bwt od IV x 3days + IVMP**
Cyclosporin-a	**3-8 mg/kg/bwt /day POx 5-6 days depends on a febrile period (keep serum level 400-500ng/ml).**
Anakinra2-6 mg/kg/day by subcutaneous injection	

 # Plasma exchange and methotrexate/ may be the final choice for refractory KD.
*** Infliximab may be considered as preferred first line therapy in resistant KD (desired drug of Indian Societyof Kawasaki disease). Steroid may beaded as per the severity of CAL**

Table No. 11: Prediction scoring Systems forIVIG Resistant cases

1.Kobayashi score (≥5 points; sensitivity 76%, specificity 80%)		
Na	≤133 mmol/L	2

AST	≥100 IU/L	2
Day of starting treatment (or diagnosis)		
Day 4 after onset or earlier	2	
Neutrophils	≥80% 2	
CRP	≥10 mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤12 months	1

2.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	≥8 mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤6 months	1

3.Sano score (≥2 points; sensitivity 77%, specificity 86%)

AST	≥200 IU/L	1
Total bilirubin	≥0.9 mg/D	1
CRP	≥7 mg/dL	1

4.Sathoshi Sato Score (3 or >3)

Neutrophils >75%	2
IL 6 >140pg/ml	2
Il-6 70-140pg/ml	1

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 have 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. (43, 44)

Long-term Fate and Complications of Giant CAA

Although rare, giant CAA (8 mm 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 myo-intimal 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 subendothelial 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. (44,45)Thrombotic occlusions 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 gradual stenotic occlusion. (46). We should be careful in monitoring such high-risk cases with regular ECG, exercise test and echocardiogram. In acute MI or ischemia, infants or children will present as severe cry, vomiting abdominal pain even shock. Older children may complaints of chest pain. Symptoms in MI and findings in ECG are given in **Table 12.**

Table 12. Symptoms of Myocardial Infarction & ECG findings in childern

SYMPTOMS	ECG CHANGES
• VOMITING • CHEST PAIN • SEVERE CRY • SHOCK • ABDOMINAL PAIN • ARRHYTHMIA	• ST/T CHANGES; T INVERTION IN II, III, AVF • Q IN II, III, AVF INDICATE INFRACTION • PEAKED J POINT ELEVATION INDICATE ISCHEMIA • ELEVATION/ DEPRESSION OF ST SEGMENT V1-V3 • WIDE QRS >35MS, I AVL, V5, V6 • PROLONGED QTC > 480 , • VENTRICULAR TACHYCARDIA

Routine investigations in such cases with Tropi I and CKMB are necessary. therapy with tissue-type plasminogen activator (tPA) is the most commonly administered therapeutic regimen for occlusive or near-occlusive coronary artery thrombosis in infants and children. A common regimen of tPA is 0.5 mg/kg/hr over 6 hours. An alternative regimen of tPAused in adult coronary artery thrombosis, is 0.2 mg/kg intravenously (maximum 15 mg) stat, then 0.75 mg/kg over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg over 60 minutes (maximum 35 mg). It should be administered together with low-dose ASA and low-dose intravenous heparin (10 U/kg/hr) withcareful monitoring of coagulation parameters to prevent bleeding, maintaining the fibrinogen level >100 mg/dL and platelet count >50 000/mm^3. After completion of tPA, heparin dosage is increased as appropriate for age. The coronary artery thrombus should be reassessed with echocardiographicimaging after completion of the tPA infusion. (25)

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. (45, 46). All patients should be counseled in preventive care with regards to hyperlipidemia, hypertension, diabetes, obesity and physical activities.

Conclusions

Kawasaki disease is a systemic vasculitis of unknown origin and circulating immune complexes triggered by infectious or non-infectious agents have been detected in the early phase of KD, implicating that immune-pathologic mechanisms might be involved in the pathogenesis of vasculitis in KD.Dengue fever also can trigger KD if fever persists beyond the expected duration with signs and symptoms of KD. The timely diagnosis of KD may be difficult in patients aged less than 6 months because of atypical presentations. KD should always be considered in children with prolonged unexplained fever, thrombocytosis and peeling. The role of the coronary Z scores has become increasingly crucial for managing and following up patients with KD. Gold standard therapy for acute phase of KD is IVIG and aspirin, but add on therapy will certainly mitigate the severity of coronary vasculitis. In resistant cases, KD society recommends infliximab as the first line. IVIG plus low-dose prednisolone are both reasonable choices of treatments for patients with refractory KD.Giant aneurysm never will resolve and need lifelong antiplatelet and anticoagulant therapy. Timely diagnosisand an effective risk-stratified treatment regimen can reduce the incidence of coronary artery abnormalities.Long term follow up and parenteral counsellingis most essential.

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