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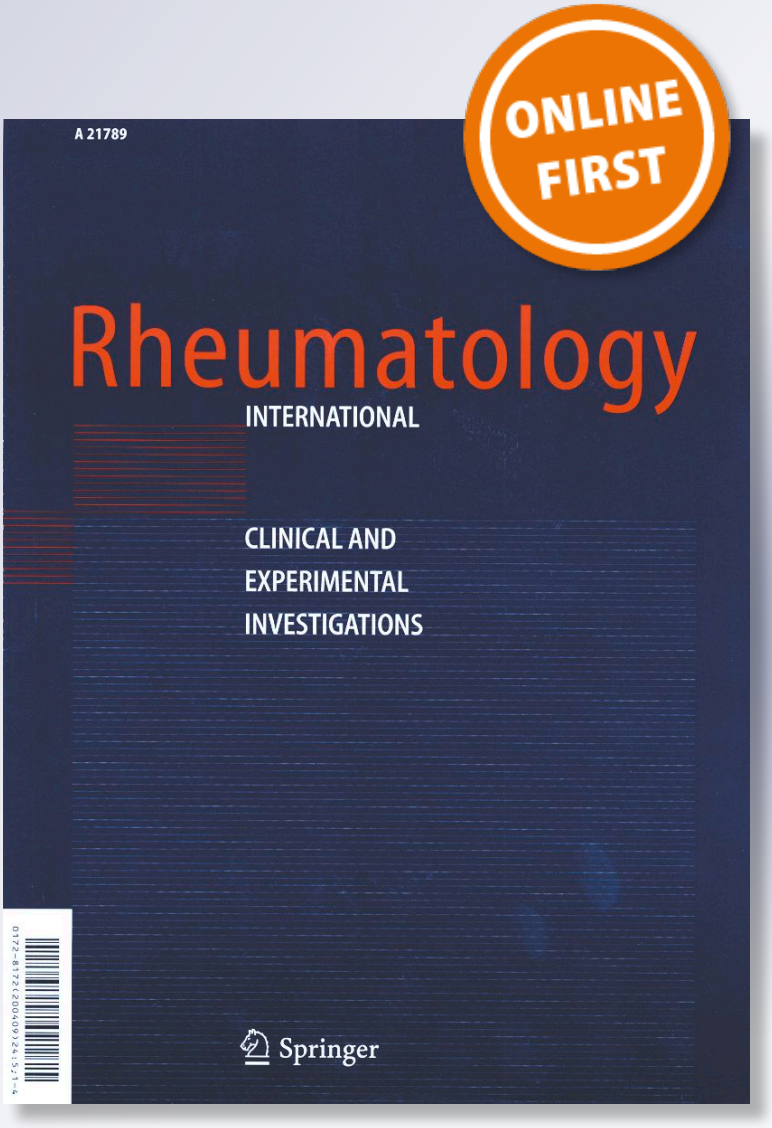
Rheumatology International
Clinical and Experimental Investigations

ISSN 0172-8172

Rheumatol Int
DOI 10.1007/s00296-012-2521-2



Springer

Rheumatol Int
DOI 10.1007/s00296-012-2521-2

ORIGINAL ARTICLE

Orange–brown chromonychia, a novel finding in Kawasaki disease

Priyankar Pal · Prabhas Prasun Giri

Received: 7 March 2012 / Accepted: 23 August 2012

Abstract Kawasaki disease (KD) is one of the commonest vasculitis of childhood, where diagnosis is clinical based on a plethora of signs and symptoms. One of the typical findings is the changes in the extremities including the nail changes. Orange–brown chromonychia is a colour change in the nails which has been observed in some cases of KD. Here, we report a series of 40 patients of KD, where a typical transverse orange–brown discolouration of nails or chromonychia was noted in 29 patients. Though chromonychia is noted in many other rheumatic and nonrheumatic diseases, the typical transverse orange–brown chromonychia observed in KD patients can be included as an additional clinical feature in diagnosis of KD.

Keywords Kawasaki disease · Orange–brown chromonychia · Nail changes

Abbreviation
KD Kawasaki disease

Introduction

Nails, particularly fingernails, may show signs that are important not only for detection of diseases of the nails itself, but also of diseases of other organs or the system as a whole. Changes in colour of nail plates or nail beds seem to suggest the parts are windows to what is happening inside the body. Chromonychia is a term used to indicate an abnormality in colour of the substance and/or surface of the nail plate and/or subungual tissues [1]. Many diseases and drugs are associated with chromonychia. But association with Kawasaki disease (KD) is relatively a new observation. In our case series, almost 75 % of KD patients presented with orange–brown chromonychia.

Patients and methods

Clinical records of children aged below 10 years who fulfilled the diagnostic criteria of KD and admitted at the Institute of Child Health, Kolkata during the time period of April 2009 to April 2011 were reviewed. The diagnosis of KD was based on the typical clinical findings with the help of relevant laboratory investigations and exclusion of other diseases. The data collected included details of clinical and laboratory features, treatment and outcome. The patients with chromonychia was registered and closely followed up.

Results

Amongst the 40 children with KD, orange–brown chromonychia was noted in 29. In all the cases, this transverse orange–brown discolouration of finger and toe nails started appearing between 5th and 8th day of onset of fever. The chromonychia migrated distally as the nails grew. At around 2 weeks, it begins to fade with complete disappearance over the next 7–10 days. The colour change is better appreciated in the finger nails rather than the toe

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Published online: 15 September 2012

nails. There was no evidence of any other disease or drugs that could lead to chromonychia (Figs. 1, 2, 3).

Discussion

Kawasaki disease is an acute febrile vasculitic syndrome caused mainly by the affection of the medium- and small-sized blood vessels. Amongst the clinical features of the disease, there are few typical nail changes that have been well described; commonest being the periungual desquamation and the transverse leukonychia (Beau's lines) [2]. There are also few case reports regarding onycholysis in KD. Ciastko reported onychomadesis (spontaneous separation of the nail from the matrix) of all 20 nails in an 8-year-old boy with KD, which started 1 week after periungual desquamation [3]. The proximal nails subsequently grew normally, with minimal evidence of residual scarring. Spontaneously resolving pincer nail deformity (transverse curling of the nail along its longitudinal axis) [4] in an infant with KD and leukonychia partialis [5] (abnormally white proximal portion of the nail) have also been reported. These nail abnormalities are nonspecific and, in the context of KD or other systemic triggers, generally resolve spontaneously within 1–2 months.

Chromonychia or abnormal colour of nails is described following the use of antineoplastic drugs with few distinct forms, the most frequently seen is melanonychia [6]. Although a few cytostatics may cause these changes, the drugs most commonly involved are adriamycin, cyclophosphamide and vincristine, or in polychemotherapy [7], thermal injury, contact exposure to elemental iron, angiotensin-receptor blockage therapy, use of nail hardener, and in association with systemic lupus erythematosus and hyperbilirubinemia. Green chromonychia has been reported in association with *Pseudomonas* infection [8]. Chromonychia is also associated with AIDS, significant ($p < 0.05$) being with CD4 counts below 200 per cubic millimetre [9].

The transverse orange–brown chromonychia in relation to KD is relatively a novel finding. Lindsley was the first to describe this unusual red transverse nail-bed lines in four patients with KD [2] followed by Thapa et al. [10] who described this in two cases. But no large case series was published earlier with these findings. The reported children had transverse orange–brown chromonychia of all 20 nails, which developed during the late acute phase or early subacute phase of KD, and sometimes were replaced by transverse leukonychia. A careful literature search failed to reveal such large observation of chromonychia in KD.

However, it needs to be mentioned that similar orange–brown chromonychia has also been observed in other rheumatological diseases like systemic arthritis and

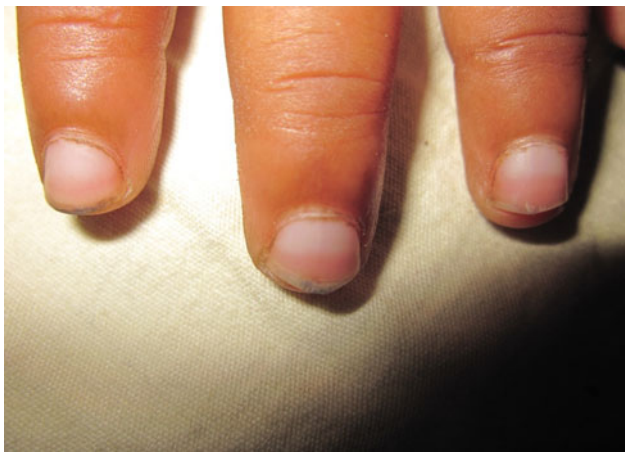

Fig. 1 Orange brown chromonychia of fingers during acute stage

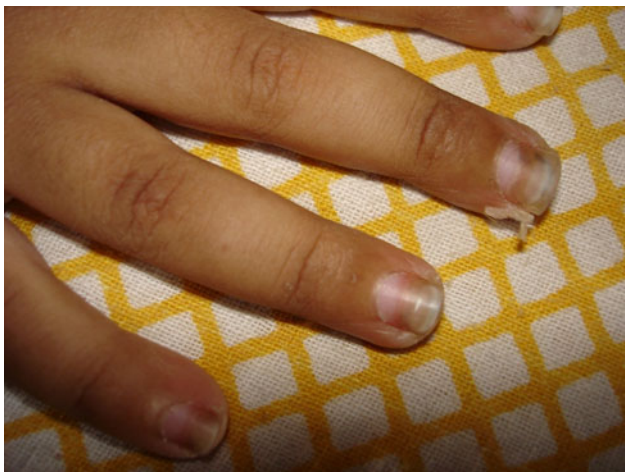

Fig. 2 Chromonychia of fingers during subacute Kawasaki disease with desquamation

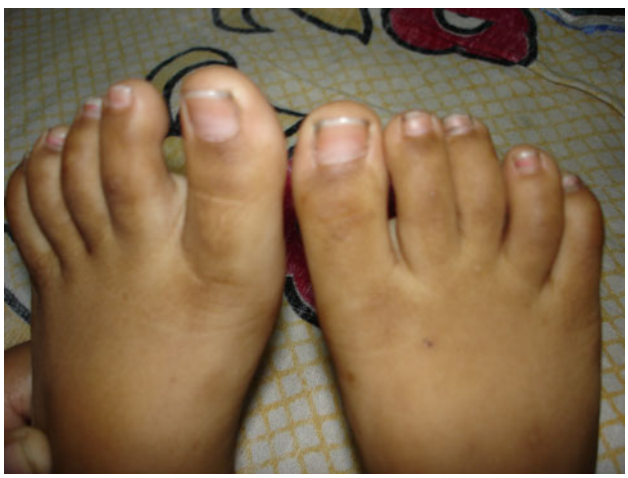

Fig. 3 Chromonychia involving toe nails

hemophagocytic lymphohistiocytosis. Now, individually none of the clinical features of KD is unique to the disease. But, observed together or sequentially they form a pattern that is diagnostic. Our suggestion is to incorporate orange–brown chromonychia as an add-on clinical finding to the existing armamentarium.

Conflict of interest None.

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Nephrotic Syndrome in Kawasaki Disease

Clinical Pediatrics
XX(X) 1–2

DOI: 10.1177/0009922813499068
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Introduction

Kawasaki disease (KD), or mucocutaneuous lymph node syndrome, was first reported by Dr Tomisaku Kawasaki of Japan in 1967. Currently, KD is known to have a worldwide distribution as a common disease predominantly affecting children younger than 5 years. KD is the most common cause of multisystem vasculitis in children. The vessels most commonly damaged are the coronary arteries, making KD the number one cause of acquired heart disease in childhood.

Case Report

A 4.5-year-old previously healthy female child presented with fever (104°F) for past 7 days, with nonpurulent bulbar conjunctivitis, mucositis, unilateral cervical lymphadenopathy, edema of the acral parts of the limbs, and excessive irritability. She also had a 5 cm liver, diffuse maculopapular rash, chromonychia, and greenish stool. The child was sick looking, febrile, irritable, and without any sign of heart failure. A pulse rate of 139/minute, blood pressure of 102/74 mm Hg, and a room air saturation of 100% was all that we found. Chest was bilaterally clear and no murmur in the heart could be discerned. Blood tests revealed leukocytosis (14 300/mm^3) with a neutrophilic preponderance, elevated erythrocyte sedimentation rate 95 in first hour, high C-reactive protein (43.2 mg/L), and normal serum creatinine (0.3 mg/dL), acute anemia (7.6 g/dL), and thrombocytopenia (94 000/mm^3). Serum sodium of 129 mmol/L, potassium 4.3 mmol/L, total protein 4.4 g/dL, and albumin 1.8 g/dL with 14 to 16 pus cells/high-power field in urine, and significant proteinuria (++) were noted. Chest X-ray was normal, and urine and blood cultures were sterile. The child was diagnosed as a case of KD and intravenous immunoglobulin transfusion was started with a dose of 2 g/kg in a single dose. Aspirin was also added along with immunoglobulin. Fever subsided within 24 hours of starting intravenous immunoglobulin transfusion, but the edema of the hand and foot increased over time and the child also developed ascites with anasarca within the next 48 hours. Serum albumin was found to be significantly decreased (1.3 g/dL) and the ultrasonography of abdomen showed ascites with a normal-sized kidney, with normal echogenicity, and a normal corticomedullary differentiation. Serum triglyceride was high (197 mg/dL) and urine protein was (++++), with a urinary protein creatinine ratio of 107. Serum C3 and C4 levels were normal and infection serology (human immunodeficiency virus, hepatitis B surface antigen, hepatitis C virus) was negative. Echocardiography revealed multiple valvular involvement with trivial tricuspid and mitral regurgitation. So it was diagnosed as a case of nephrotic syndrome in KS. But the patient was not put on steroids and was kept on observation. The edema gradually subsided and the urine became negative for protein ~~in~~ 9 days of immunoglobulin transfusion. The patient was discharged after 13 days of hospital admission, and in follow-up echo, the heart was found to be normal and there was no relapse of nephrotic syndrome in next 1 year.

Discussion

All the cases previously reported had some kind of complications. ~~The~~ 4-month-old Japanese girl[1] had steroid-resistant nephrotic syndrome and her renal biopsy demonstrated a diffuse mesangial proliferative glomerulonephritis with microcystic tubular dilatation. She ultimately died of chronic renal failure at the age of 11 months. In 1989, the first case reported by Lee et al[2] was a 3-month-old infant with KD presenting with ~~nephritic~~ syndrome during the acute phase of the illness, which improved under steroid therapy. However, the patient died from acute myocardial infarction due to coronary aneurysm. Krug et al[3] reported 3 cases of KD, where 1 child developed acute renal failure and the other presented with features of hemodynamic shock. But our case had all the typical features of KD, ~~but~~ did not

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develop any other complication but nephrotic syndrome and responded rapidly to treatment with intravenous immunoglobulin.

Kawasaki disease is a self-limiting systemic inflammatory disease that occurs predominantly in children younger than 5 years.Clinical manifestations of KD include prolonged fever (1-2 weeks, mean 10-11 days), conjunctival injection, oral lesions, polymorphous skin rashes, extremity changes, and cervical lymphadenopathy, all of which comprise diagnostic criteria. In addition, arthritis, aseptic meningitis, anterior uveitis, gall bladder hydrops, urethritis, and lung involvement can be seen. Some more severely affected patients show cardiac complications, particularly coronary artery lesions, such as aneurysms and ectasias, which develop in approximately one quarter of untreated children and 5% to 10% of intravenous immunoglobulin–treated children. These diverse systemic inflammations (mainly vasculitis) may be caused by inflammatory mediators with circulating immune cells (neutrophils, lymphocytes, natural killer cells, and monocytes), and there may be various immune cell infiltrations in all affected pathologic lesions from affected lymph nodes to skin rashes. Particularly, a larger number of T cells (more CD8 cells than CD4 cells), large mononuclear cells, macrophages, and plasma cells, with a smaller number of neutrophils, are observed in various organ tissues of fatal cases of acute KD.[4]

Primary idiopathic nephrotic syndrome is a frequent source of morbidity in children. In a minority of cases, mutations in podocyte genes[5] explain proteinuria. Pathogenesis, however, is unknown for the major group of patients who do not present molecular defects, in which case a general problem has been proposed linked to T cell immunity.[6] Multiple independent observations point to the involvement of free radicals of oxygen (reactive oxygen species) in proteinuria deriving from an altered regulation by regulatory T cells of polymorphonuclear neutrophil burst. In fact, reactive oxygen species production by polymorphonuclear neutrophil in children with idiopathic ~~nephritic~~ syndrome is increased 10-fold and correlates with proteinuria.[7] Oxidants are toxic for the kidney in humans and in animals, and when oxidant production overcomes the intra- and extracellular defenses, it leads to renal damage.[8]

So we can conclude that nephrotic syndrome can be one of the renal manifestations of KD and it can be hypothesized that a common immune-mediated damage is responsible for both[9,10] these manifestations. We have also observed that treatment of KD with intravenous immunoglobulin is sufficient, and the associated nephrotic syndrome resolves spontaneously without the need of any steroid therapy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.[AQ: 3]

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.[AQ: 4]

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Indian Academy of Pediatrics Position Paper on Kawasaki Disease

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PII: S097475591600188

ABSTRACT

Objective: To formulate practice guidelines on diagnosis and management of Kawasaki disease (KD) for Indian children. **Justification:** KD is a systemic vasculitis that predominantly affects infants and children less than 5 years of age. Coronary artery abnormalities (CAA) develop in around 15-25% of untreated children with KD. Coronary artery involvement can lead to long-term cardiovascular implications such as development of premature coronary artery disease. Diagnosis of KD is essentially clinical based on recognition of a constellation of characteristic symptoms and signs. Timely diagnosis and initiation of intravenous immunoglobulin (IVIg) therapy is known to produce five-fold reduction in the incidence of CAA. As there is no confirmatory laboratory test for KD, the diagnosis may be missed if one is not familiar with the nuances of clinical diagnosis. **Process:** A committee was formed under the auspices of Indian Academy of Pediatrics in early 2018 for preparing guidelines on KD in Indian children. A meeting of the consultative committee was held in Mumbai, and a draft protocol was devised. All members scrutinized the recent publications on the subject and an attempt was made to arrive at a broad consensus. Published guidelines on the subject were also reviewed. **Recommendations:** The diagnosis is clinical and is aided by laboratory and 2D echocardiography. First line of therapy is IVIg, and should be started expeditiously once the diagnosis is made.

Keywords: *Coronary artery abnormalities, Diagnosis, Intravenous Immunoglobulin, Infliximab, Management.*

Kawasaki Disease (KD) is an acute febrile illness that commonly affects children below 5 years of age. Classified under predominantly medium vasculitides, it has a predilection to involve coronary arteries. Ever since the first report by Dr Tomisaku Kawasaki from Japan in 1967 [1], the disease has been increasingly reported worldwide. KD has become one of the leading causes of acquired heart disease among children in many developed countries.

Incidence of KD has been increasing significantly over the last decade possibly due to a combination of an actual increase in incidence and also due to heightened awareness amongst the Pediatricians [2]. A high index of suspicion supported with relevant laboratory tests and imaging (2D echocardiogram) is often needed in establishing the diagnosis. Though various consensus guidelines are available for diagnosis and management of KD, a nation-wide consensus for a resource constrained setting like ours is the need of the hour.

PROCESS

A National Consultative Group was constituted under the auspices of Indian Academy of Pediatrics (IAP) in March 2018 for preparing the guidelines on KD in Indian children. This group of experts consisted of Pediatricians , Pediatric Rheumatologists and Pediatric Cardiologists known for their

expertise and experience in treating KD across the country. A meeting of the consultative committee was held in Mumbai in March 2018 to discuss the scientific contents. During the daylong deliberations, the members reviewed the available literature and discussed various aspects of forming the guidelines .and a draft protocol was devised. This was reviewed and scrutinized by all the members and a final draft recommendation was formed through a virtual meeting .The draft recommendations formulated by the group were circulated among the members and a consensus document was finalised.

DIAGNOSIS

We have two established criteria that could be used as a guide for diagnosis of KD- The American Heart Association (AHA) criteria [1] and the Japanese criteria [7]. AHA criteria have been discussed in this document and are detailed in ***Box* I**.

Clinical Features

Through history and assessment of clinical findings play a major role in the diagnosis, as there are no specific tests.

Principal Clinical Findings

Diagnosis of KD is usually made on the basis of fever for ≥5 days along with the history/presence of ≥4 out of the 5 key clinical features. Diagnosis is made as per features given in ***Box* I** but the presence of classic clinical presentation or coronary artery abnormality, the diagnosis of KD can be made in less than 5 days.

Fever: The most common manifestation is fever, which is often high grade and remittent type. If untreated, fever continues for 1-3 weeks and resolves spontaneously by 3 to 4 weeks, mean duration of fever being 11 days.

Conjunctival injection: Bilateral, painless and non-exudative conjunctival injection with peri-limbal sparing usually begins in first few days after fever onset, seen in 80-90% cases. Slit lamp examination might reveal anterior uveitis during the first week of fever. Purulent conjunctivitis should suggest alternate diagnosis.

Oral changes: Bleeding, crusting, dryness, erythema and fissuring of lips are common mucosal changes noted in KD patients. Oral mucosal and pharyngeal erythema can also be seen. Erythema of tongue along with the presence of prominent papillae results in a strawberry tongue appearance.

Cervical lymphadenopathy: Cervical adenopathy is usually non-specific and the least common clinical finding. Unilateral enlargement of a cervical node ≥1.5 cm diameter in the anterior triangle of neck may be noted. Occasionally the lymph node mimics suppurative lymphadenitis and may be associated with retropharyngeal / parapharyngeal edema (phlegmon) mimicking a retropharyngeal abscess on MRI. But presence of associated clinical features of KD helps in clinching the diagnosis.

Rash: A maculopapular erythematous rash that begins in trunk, later extending to extremities and face, is usually seen by 5 days of onset of the illness. Sometimes it resembles a scarlatiniform,

erythroderma, erythema multiforme, or urticaria like rash. Bullous, vesicular or petechial rashes are usually not seen and suggests an alternate diagnosis.

Extremity changes: During the acute phase, erythema of palms and soles along with edema and induration of hands and feet may be seen. Desquamation of fingers and toes usually occurs 10-20 days after the onset of fever and typically starts in the periungual region. It may extend to involve the entire palm and sole.

Other Clinical Findings

Perianal or perineal desquamation is typically seen during the acute phase of KD, as early as day 6 of fever and is a useful clinical pointer.

Reactivation of BCG scar: Erythema and induration can occur at the site of BCG scar. Though noted in a small proportion of children with KD, it is virtually pathognomonic when other findings are missing [1].

Nervous system: Irritability is a common finding especially marked in infants. It is usually out of proportion to the degree of fever and thought to be a manifestation of aseptic meningitis. Profound sensorineural hearing loss may be present. Facial palsy, though rare, has been well documented. Prolonged unexplained fever with extreme irritability may be the only clinical manifestation in many infants below 6 months of age without any of the principal clinical signs of KD.

Gastrointestinal system: Diarrhea, vomiting, pain abdomen, hepatitis, pancreatitis and gallbladder hydrops can be present.

Genitourinary system: Urethritis/meatitis is a common feature in the acute phase presenting as sterile pyuria. Less common features are hydrocele and phimosis.

*Musculoskeletal system***:** Pain and swelling of interphalangeal joints may occur during the acute phase. Arthritis of large joints (knees and ankles) usually occur during the convalescent phase and is seen in 10-15% of cases.

Respiratory system: Tachypnea, dyspnea, and cough may rarely be seen. Chest radiograph may reveal peribronchial or interstitial infiltrates.

Cardiovascular: Pericarditis, myocarditis, valvular dysfunction, congestive heart failure, and peripheral gangrene are the cardiovascular manifestations of KD.

About 5% of children may present with cardiovascular collapse and shock that may be difficult to differentiate from toxic shock [8,9]. High index of suspicion and presence of accessory clinical features helps in clinching the diagnosis. KD shock is readily responsive to IVIg which helps in differentiating from a viral myocarditis.

Beau lines: Transverse grooves in the nails can be noted 1-2 months after the onset of illness indicating a catabolic process in the preceding weeks.

Definitions used in KD diagnosis are provided in ***Box* II**, and approach to a child with suspected KD is shown in ***Fig.* 1**.

Laboratory Tests

Diagnosis of KD is about pattern recognition with impetus being on a good history and detailed physical examination. Laboratory tests are non-specific and are only supportive and laboratory findings vary with the course of illness.

Hemoglobin: Mild to moderate normocytic, normochromic anemia is common.

Leucocyte count: Leukocytosis is usually seen in acute phase of illness with neutrophilic predominance.

Platelet count: Thrombocytosis is one of the significant lab findings in KD. Platelet count starts rising after first week, reaching a peak in the third week and normalizing by 4-6 weeks. Thrombocytopenia is uncommon but can occur in first week. Thrombocytopenia is a risk factor for development of CAA and may be a marker of incipient macrophage activation syndrome [10,11].

Acute phase reactants like Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are almost always elevated in KD. IVIG therapy by itself can cause an elevation in ESR leading to doubts in the mind of the treating physician. Hence, CRP is more useful to assess response to treatment with IVIG. Macrophage activation syndrome which can rarely complicate KD should be suspected in patients with severe clinical disease associated with minimally elevated ESR and markedly elevated CRP. It might be prudent to look for an elevated serum ferritin to confirm this suspicion.

Serum transaminases: Mild to moderate elevation is seen in around 50% of patients.

Serum albumin: Hypoalbuminemia is often noted in the acute phase suggesting severe inflammatory process.

*Sterile pyuria (>10 cells/high power field with sterile cultures)***:** This is due to urethritis and sometimes be mistaken for urinary tract infection in infants.

Procalcitonin levels are usually normal, but elevated levels are associated with increased risk of IVIg resistance and CAA [12]. Serum Pro-BNP (Pro-brain natriuretic peptide) and N terminal Pro BNP (NT-ProBNP) levels are elevated in KD and can serve as useful biomarkers in distinguishing incomplete KD and closely mimicking febrile illnesses. Serum levels of NT-Pro-BNP > 225 pg/mL can assist in the diagnosis of KD (suggesting myocardial dysfunction) (86.5% sensitivity and 94.8% specificity) [13]. ECG may reveal evidence of myocarditis and conduction disturbances. An ultrasound of the abdomen may show hepatomegaly, hepatosplenomegaly, acalculous cholecystitis (gall bladder hydrops).

Echocardiography

Echocardiography is the imaging modality of choice for diagnosis, risk stratification, treatment planning, prognostication and follow-up of any suspected or confirmed KD. KD is a clinical diagnosis and role of echocardiography is to only confirm/exclude cardiac involvement especially coronary arteritis. Thus, treatment of KD should not be withheld for local non-availability of pediatric

cardiologist. Simultaneously, the pediatrician should refer to the pediatric cardiologist if pyrexia of unknown origin lasts longer than 7 days.

Objectives of echocardiography in KD are:

- To confirm the diagnosis in case of suspected incomplete KD, though a normal echocardiogram does not exclude the diagnosis.
- To quantify coronary changes in proven KD.
- To look for other cardiac complications like myocarditis and cardiovascular collapse (5%), valvular regurgitation (*e.g.,* mitral regurgitation), pericardial effusion [1,8,9].
- To assess response to therapy by serial echocardiography (regression, persistence or progression of aneurysm, myocarditis and valvular dysfunction).
- To look for myocardial ischemia secondary to coronary involvement, usually seen in giant/large aneurysms.
- Rarely rupture of aneurysm with cardiac tamponade especially in acute phase with rapid enlargement of aneurysm.
- Prognostication and counselling of family.
- Long term follow-up of KD with persistent CAA.

Echocardiographic Changes in KD

The cardiac involvement in KD can be grouped into a) Early changes b) Subacute Changes c) Late changes.

a) *Early changes (1st week of fever):* Coronary changes are uncommon in the first week. The important clues are myocarditis (prevalence 50-70%), pericarditis, small pericardial effusion and transient mild to moderate mitral regurgitation (23-27%). We recommend use of advanced echo modalities like myocardial performance index and tissue Doppler to document myocarditis in addition to standard parameters like Ejection Fraction (EF) and Fractional Shortening (FS) [14,15].

7% of children with KD in US present with cardiovascular collapse (KD shock syndrome). The unique features of KD myocarditis are 1) it presents early 2) precedes coronary arteritis, 3) transient and resolves earlier than other causes of myocarditis as inflammation and myocardial edema subside. In doubtful cases, serum NT pro BNP may be used as a surrogate marker, although it is nonspecific and cut off values yet to be clearly defined [13,16,17].

We reiterate that normal coronaries in the first week do not exclude KD.

b) Subacute changes (after 1st week of fever): The highlight of this phase is detection of coronary involvement and its aftermath.

Some tips and clues for successful echo in KD child are given in ***Box* III**. The coronary involvement as per z score classification is as follows [1]:

- No involvement: z score always <2
- Dilatation only: 2 to < 2.5

Aneurysms as per size:

- Small CAA: ≥2.5 to <5
- Medium CAA: ≥5 to <10 and absolute dimension <8mm
- Large /Giant CAA: ≥10 or absolute dimension ≥ 8mm

Aneurysms as per shape: saccular or fusiform

The Heart Beyond the Coronaries

Apart from early phase, ECHO during the subacute and long term phases should focus also on:

- Aortic root dilatation and aortopathy
- Cardiac valves: Late onset regurgitation is attributed to fixed damage to valve apparatus by the inflammatory mechanism.
- Myocardial function: Both global and regional wall motion abnormalities (RWMA) perfused by particular coronary territories are to be reported. Abnormal RWMA is a clue of myocardial ischemia and prompts further analysis by CT or direct coronary angiography.

How frequently should one repeat Echo in a child with KD?

- At diagnosis.
- Uncomplicated patients**:** 1-2 weeks and also 4-6 weeks after treatment. This is because dilatation is unusual beyond 6 weeks. Normal coronaries may be discharged from cardiology care after 12 months but the medical records should permanently mention the diagnosis of KD.
- For significant and evolving coronary abnormalities: At least twice per week till luminal dimensions stabilize and we should look specifically for thrombus. After that at 2 weeks, 4-6 weeks, 3 months and then every 6 -12 months till parameters normalize.
- To detect coronary artery thrombosis it may be reasonable to perform echocardiography for patients with thrombus at diagnosis, expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset, as failure to escalate thromboprophylaxis is a primary cause of morbidity and mortality.

Long term cardiac assessment in KD

Long-term status is when the patient is stable after the acute illness and the coronary artery luminal dimensions are not increasing or progressing (usually within 15 to 45 days).

- 5% of acute coronary syndrome in US has been attributed to “missed KD in childhood” [18,19].
- Normal coronaries at initial presentation usually have no long term sequelae.
- Small or moderate aneurysms usually demonstrate normalization of luminal dimensions, infrequently stenosis may happen. Development of late aneurysms especially with coexistent stenosis is also reported especially with repeat KD or suboptimal initial treatment.

- Coronary artery events (thrombosis, stenosis, intervention, MI, death) occurred in 1% of those with an aneurysm Z score <10 and an absolute dimension <8 mm, in 29% of those with a Z score ≥10 but an absolute dimension <8 mm, and in 48% of those with both a Z score ≥10 and an absolute dimension ≥8 mm [20, 21].
- Subclinical functional impairment (fibrofatty changes, necrotic core and calcification) of these coronaries have been observed with advent of intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Interestingly wall thickening was found more in those coronaries where aneurysms normalized on longitudinal follow up. PET scan shows increased uptake in these areas [22-24]. Clinically these translate to impaired myocardial flow and reduced response to traditional coronary vasodilators like nitroglycerin. This poses a risk to myocardial infarction in KD survivors.

Limitations of echocardiography: Despite its primary position as a diagnostic modality for KD, echocardiography has some limitation:

- Abnormal coronaries are seen in only 20- 25% of KD. Hence, a normal echo does not preclude KD [1].
- Coronary artery aneurysms usually appear after 1st week. It must be repeated in all KD patients after 2 & 6 weeks [1].
- Cardiac sequelae in classical and incomplete KD are same. So, cardiologist has to be more meticulous while imaging suspected atypical KD because diagnosis rests on 2 D echo and laboratory findings.

Role of Other Cardiovascular Imaging Modalities

- *Acute phase***:** Echocardiography is the best modality.
- *Medium and long term phase***:** As the child grows, transthoracic echocardiography may not be able to visualize especially the distal coronary segments. Apparent normalization of coronary diameters may also be due to intimal calcification and fibrofatty changes. So, use of CT coronary angiography, PET scanning, cardiac MRI and documenting inducible myocardial ischemia (Dobutamine stress echocardiography, stress thallium scan, PET) to assess myocardial function and ischemia in older children, adolescents and adult survivors is recommended. Exercise TMT alone is not sufficient to detect these changes. If any of these are positive, direct coronary angiography as a planner for subsequent angioplasty or bypass surgery is to be done.

Differential Diagnosis

- *Infections*: Bacterial (Streptococcal, Leptospirosis, Rickettsia), Viral (measles, adenovirus, Epstein Barr virus).
- *Toxin related:* Staphylococcal Scalded Skin Syndrome, toxic epidermal necrolysis
- *Inflammatory*: Systemic Juvenile idiopathic arthritis

- *Drug hypersensitivity*: Steven-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS), mercury hypersensitivity.

Gastrointestinal features like paralytic ileus, gall bladder hydrops, greenish diarrhea, jaundice and raised transaminases may mimic other gastrointestinal infections or surgical conditions. Sterile pyuria and CSF pleocytosis can masquerade as urinary tract infection or aseptic meningitis.

A fever that does not appear to respond to antimicrobials should always raise the consideration of alternate pathologies like inflammatory or vasculitic illness like KD.

TREATMENT

Acute Kawasaki Disease

The goal of treatment is to control the acute inflammation and prevent long term coronary sequelae. IVIg and high-dose aspirin are the cornerstones in the management of KD, although the role of high-dose aspirin in the acute stages is debatable. Treatment should be initiated promptly and must not be delayed awaiting echocardiography, when the clinical features are suggestive of KD.

Single dose of IVIg 2g/kg administered over 12-24 hours should be given within 10 days of illness, preferably in the first 7 days [1]. Timely administration of IVIg reduces the development of CAAs from 15-25% to 3-5%, and the risk of giant aneurysms to 1% [1].

IVIg should be considered even in patients with >10 days of illness with persistent fever, systemic inflammation evidenced by elevated ESR or CRP (>3.0 mg/L), or presence of CAAs. IVIg may not be needed in patients who had resolution of fever with normal inflammatory parameters and normal echocardiography findings [25].

Dose of aspirin used in the acute stages is 30-50 mg/kg/day in 3-4 divided doses, that is continued until the patient is afebrile for 48 hours. The dose of aspirin (ASA) is reduced to 3-5 mg/kg/day and continued for 6-8 weeks and stopped if CAAs are not detected in the 6^{th} week echocardiography. The anti-platelet dose of aspirin is continued in patients who have persistent CAAs until the normalization of coronary artery dimensions. Patients on long-term aspirin need influenza vaccination yearly to reduce the risk of Reye's syndrome.

Multiple studies have come up recently, demonstrating the beneficial use of corticosteroids along with IVIg in children predicted to have an increased risk of CAAs and IVIg resistance [3]. Addition of glucocorticoids (prednisolone) to IVIg has been shown to reduce the risk of CAAs, duration of fever, and inflammation in Japanese children who are at a high risk for resistance to IVIg therapy. A recently published Cochrane database systemic review has even suggested that a long course of steroids along with IVIg should be considered in all children with KD until further evidence are available [26].

Recommended use of steroids in KD: Oral prednisolone (2mg/kg/day) to be initiated with IVIg and gradually tapered over 15 days after normalization of CRP levels.

In IVIg responsive patients, fever usually subsides by 36-48 hours along with decrease in inflammatory parameters. Patients with recurrent KD, defined as a repeat episode of KD after complete resolution of the first episode, should receive standard therapy with IVIg and ASA.

Anticoagulation in Kawasaki disease is indicated in the following situations:

a. Giant aneurysm, multiple or complex aneurysms, presence of thrombus
b. Associated stenosis
c. Peripheral gangrene

It is prudent to initiate with LMW heparin followed by oral warfarin to maintain INR of 2-2.5. However in view of the difficulty of maintaining the target INR in children on oral anticoagulants, one may consider continuing long term thromboprophylaxis with LMW heparin only after proper parental counselling.

For arterial thrombosis/peripheral gangrene- thrombolytic therapy has been tried in addition to anticoagulation.

Treatment of incomplete KD: Incomplete forms should be treated in the same manner as complete KD.

Resistant KD

Children who have persistence or recurrence of fever 36 hours after the end of IVIg infusion are considered to be IVIg resistant [1]. Around 10 to 20% of patients are IVIg resistant [27]. Prolonged fever and unresponsiveness to the first dose of IVIg are significant risk factors for CAAs.

Risk scores for predicting non response to IVIg: Egami [28], Sano [29] and Kobayashi [30] scoring systems are some of the scoring systems that have been shown to predict IVIg resistance.

There is no established consensus on the pharmacologic treatment of refractory KD. Various therapeutic options available -

- *IVIg retreatment*: Many experts recommend retreatment with second dose of IVIg 2g/kg. Rate of refractoriness to the second dose IVIg is around 22-49% [31].
- *Corticosteroids*: Furukawa et al compared the effectiveness of second dose IVIg and IV prednisolone in patients with IVIg resistant KD. They found that incidence of CAA and treatment failure were similar between 2 groups, however, the steroid group had a faster defervescence of fever and improvement in inflammatory markers [32] The AHA recommends that a short duration of high-dose glucocorticoids could be a reasonable treatment option in patients with IVIg resistant KD [1].
- *Infliximab:* Infliximab is a chimeric monoclonal anti TNFα antibody. Dose is 5 mg/kg given intravenously over 2 hours. Studies have not demonstrated superiority of infliximab over others in IVIg-resistant KD in terms of coronary artery outcomes though fever and other constitutional features resolve well. The AHA recommends the use of infliximab as a substitute for a 2nd dose IVIg or steroids in resistant KD [33,34].

- *Cyclosporine:* Cyclosporine inhibits lymphocyte activation by blocking the NFAT-calcineurin pathway that is thought to influence disease susceptibility and development of CAAs in KD [35]. The AHA recommends the use of cyclosporine as a possible third or fourth-line therapy in patients with KD.
- *Plasma exchange:* Used rarely for children who have active inflammation despite multiple doses of IVIg, corticosteroids, and infliximab.
- *Cytotoxic agents*: Cyclophosphamide is used to treat other severe vasculitides, but the risks of cytotoxic agents limits its use.
- *Statins*: Statins, hydroxymethylglutaryl coenzyme A-reductase inhibitors, have been shown to reduce cholesterol levels as well as improve surrogate markers of atherosclerosis and cardiovascular disease. Huang, *et al*. [36] reported that short-term (3 months) statin treatment (simvastatin, 10 mg/day as a single dose at bed-time) in KD patients complicated with CAL. Chronic vascular inflammation is also significantly improved, as well as endothelial dysfunction, with no adverse effects. However, long-term and randomized control trials are needed before further conclusions can be made.

It has been recently reported that atorvastatin is able to inhibit critical steps (T cell activation and proliferation, production of the pro-inflammatory cytokine TNF-α, and up-regulation of matrix metalloproteinase-9 and an elastolytic protease) known to be important in the development of coronary aneurysms in an animal model of KD, suggesting that statins may have therapeutic benefits in KD patients [37]. Taken together, statins may be beneficial as an adjuvant therapy in KD patients with CAL.

Management of Cardiovascular Sequelae

Coronary artery aneurysm is a potential serious cardiac complication of KD. With giant coronary artery aneurysm, there is increased risk of thrombosis, stenosis, ischemia, infarction and death [38, 39]. The goals of long-term management are to prevent thrombosis and myocardial ischemia while maintaining optimal cardiovascular health [39].

Medical therapy for myocardial protection: β- blockers used are Carvedilol, Metoprolol or Bisoprolol. They decrease the risk of myocardial infarction and death by reducing myocardial oxygen demand. ACE inhibitors or ARB's also protect against myocardial infarction and death. Statins in addition to their cholesterol lowering action have other pleiotropic effects in inflammation, endothelial dysfunction, oxidative stress, platelet aggregation, coagulation and fibrinolysis, which make them useful in the management of KD [37].

Thromboprophylaxis: Antiplatelet drugs like aspirin are commonly used in KD. In giant aneurysm or large distal aneurysms, a dual antiplatelet treatment with aspirin and Clopidogrel is preferred. Anticoagulation with Warfarin to achieve a target INR of 2-3 is used. LMWH is equally effective to Warfarin, used in young children in whom dosing with warfarin is difficult [1].

Surgical management: is rarely required in pediatric age group. It includes percutaneous coronary intervention or coronary artery bypass grafting [38].

Macrophage activation syndrome (MAS) is a dreaded complication that may rarely occur characterized by persistent fever, pancytopenia, liver dysfunction, hepatosplenomegaly, hyper-ferritinemia, hypofibrinogenemia, elevated serum lactate dehydrogenase, and hypertriglyceridemia. Prompt treatment with pulse methylprednisolone along with IVIg may result in favorable outcome [1].

KD should be diagnosed and treated by primary care pediatricians. However, involvement of a pediatric rheumatologist is required in some circumstances (***Box* IV**)

CONCLUSION

Kawasaki disease is the most common cause of acquired heart disease in children in the developed world. It is being increasingly recognized and treated in various parts of our country. Pediatricians must be aware of the varied manifestations of KD. Early diagnosis and prompt treatment can result in better outcomes.

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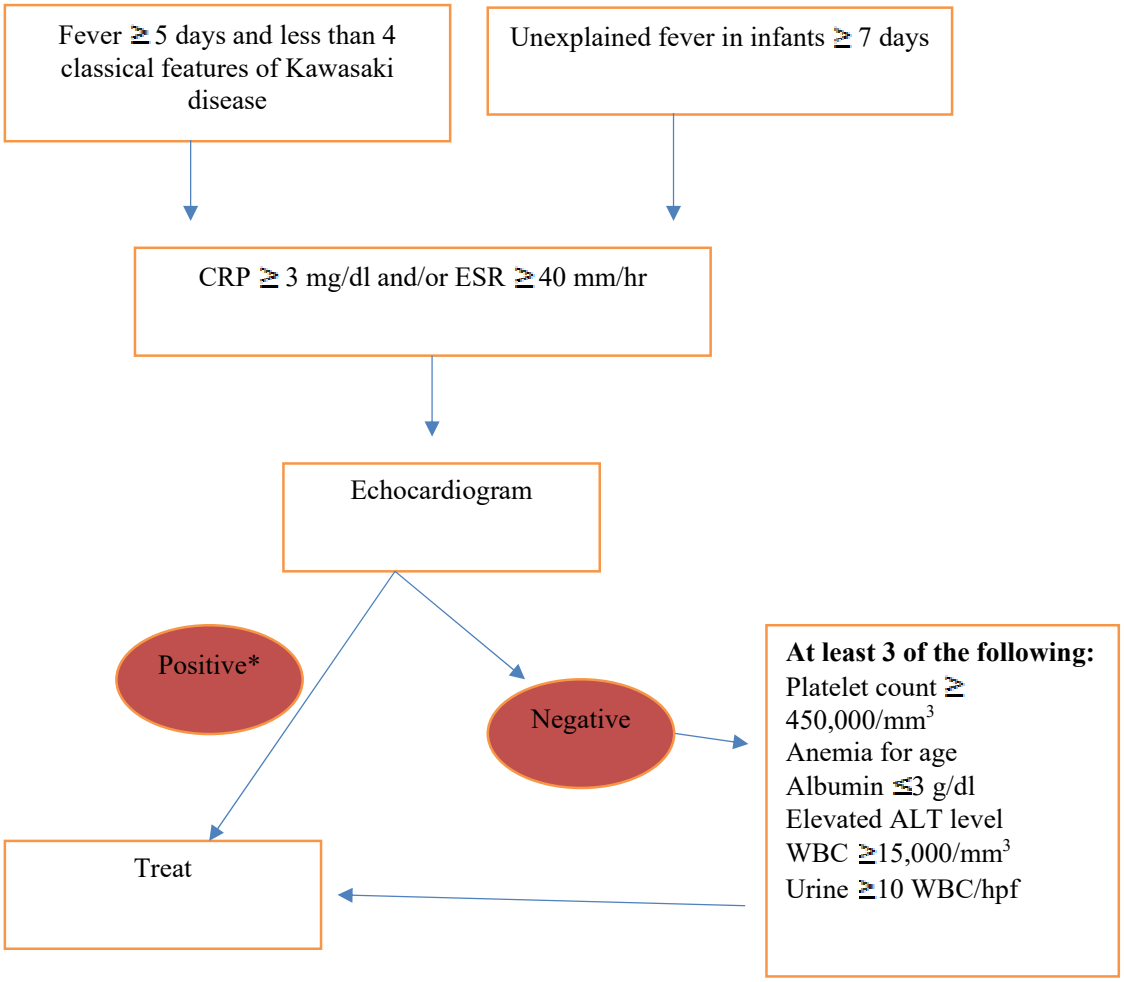
Table I Differential Diagnoses of KD and differentiating features

	KD	*Scarlet fever*	*Measles*	*SJS*	*TSS*	*SJIA*
Strawberry tongue	Present	Present	Absent	Absent	Absent	Absent
Red eyes	Present (non - exudative)	Absent	Exudative conjunctivitis	Absent	Exudative conjunctivitis	Absent
Red lips	Present	Absent	Absent	Absent	Absent	Absent
Response to antibiotics	Does not respond	Brisk response in 48 hours	NC	NC	NC	NC
Peeling	Perineal and periungual	Generalised	NC	NC	Generalised	NR
Follicular tonsillitis	Usually absent	May be present	NC	NC	NC	NC
Edema of extremities	Present	Absent	Absent	Absent	Absent	Absent
Koplik spots	Absent	NC	Present	NC	NC	NC
Oral ulcers	Absent	NC	NC	Present	NC	NC
Hepato-splenomegaly	Absent	Absent	NC	NC	NC	Present
Hypotension /renal impairment	Absent	NR	NC	NC	Present	NC
Leukocyte counts	Elevated	May be elevated	Normal	NC	NC	Elevated
ESR and CRP	Elevated	May be normal	NC	NC	NC	Elevated

NC – Not common in comparison with features in KD, SJS – Stevens Johnson syndrome, TSS – Toxic shock syndrome, SJIA – Systemic juvenile idiopathic arthritis.



(*Positive echocardiogram – refer to the section on echocardiography,

CRP – C reactive protein, ESR – erythrocyte sedimentation rate, ALT – alanine transaminase, WBC – White blood cell count).

Fig 1 Evaluation of suspected Incomplete Kawasaki Disease (Source AHA 2017)

Box I Classical Diagnostic Clinical Criteria of Kawasaki Disease by the American Heart Association [ref]
Fever persisting ≥5 day
History/presence of ≥4 principal features Changes in extremities (pedal edema in acute phase, periungual peeling in sub-acute phase) Polymorphous rash Bilateral bulbar conjunctival injection without exudates Changes in lips and oral cavity Cervical lymphadenopathy (>1.5 cm diameter)
Exclusion of other diseases with similar findings
All manifestations may not be present at the same time in a given child, as they are often transient. However, a thorough history is likely to elicit findings which maybe currently absent

Box II Definitions used in Diagnosis of Kawasaki Disease

Complete KD: Patients with fever of at least 5-day duration with presence/history of 4 or more of the 5 principal clinical findings are labelled as typical or classic KD.

Incomplete KD: Presence of fever with less than 4 out of the 5 principal clinical criteria with compatible laboratory or echocardiography findings suggest incomplete KD. Often seen in infants ≤6 months and children >6 years of age, the incomplete clinical picture often delays the diagnosis. Approach to a child with suspected incomplete KD is shown (***Fig*. 1**).

Atypical KD: Patients who along with the usual clinical features of KD also have few unusual clinical manifestations like pulmonary involvement, renal impairment are diagnosed to have atypical KD.

The terms atypical KD and incomplete KD are interchangeably used, but recent consensus is to use atypical KD in patients who have unusual clinical features and complications of KD.

Box III Tips for Successful Echocardiography in a Child With Suspected Kawasaki Disease

- Sedation should be used, as these children (especially infantile KD) are extremely irritable and toxic.
- To accurately identify coronary arteries, we recommend use of highest frequency echo transducers (10-12 Hz).
- The main coronary territories to be visualized are: left main coronary artery (LMCA) bifurcating into left anterior descending artery (LAD) and circumflex (Cx), right coronary artery (origin, mid and distal segments).
- The luminal diameter from inner edge to edge is taken in zoomed mode. Please note all measurements are to be compared with the child's body surface area. Weight and especially height are to be considered while interpreting coronary sizes. *Z* Scores are then calculated as per BSA.

Box IV Situations Where a Pediatric Rheumatologist Consultation May be Needed

- Incomplete/ atypical KD
- KD in infancy
- Presence of CAL at diagnosis
- IVIg resistant KD
- KD shock syndrome
- Suspicion of a macrophage activation syndrome

ISSN 2319-7250

Indian Journal of Paediatric Dermatology

Official Publication of the Indian Society for Paediatric Dermatology

Volume 21 / Issue 3 / July-September 2020

www.ijpd.in

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Review Article

Orange–Brown Chromonychia, a Novel Finding in Kawasaki Disease: 10 Years Since the First Publication

Abstract

Red/orange–brown transverse nail bed lines in the acute phase of Kawasaki disease (KD) was a new clinical finding reported initially in 2010. Since then, it has been universally and consistently described in the acute phase of KD and may act as an accessory clinical clue in diagnosis. This article tries to review the clinical implication and the various reports citing this finding over the last 10 years.

Keywords: *Chromonychia, Kawasaki disease, nail changes*

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"Eyes are a window to the brain." The nails though somewhat inconspicuous to the clinician, occasionally may act as reflectors of the inner maladies. Although first described by Lindsley.[1] in 1992 as unusual transverse red nail bed lines in four children with Kawasaki Disease (KD), there was no further report for the next 18 years till 2010 when "Transverse Orange–brown chromonychia in Kawasaki Disease"[2] was described in two children in *International Journal of Dermatology* as a case report from the Pediatric Rheumatology Unit of Institute of Child Health, Kolkata. The first major publication on this new entity was in 2012 in "Rheumatology International" from the same unit. "Orange–brown chromonychia, a novel finding in Kawasaki disease"[3] described forty children with KD admitted over 2 years, the nail color change being noted in 29 (72.5%). Since then, it has been described globally and has received twenty citations till date.

Chromonychia literally means colored nails. It is a term used to describe an abnormality in color of the nail plates and/or subungual tissue. Color changes in the nails have been described following the use of antineoplastic drugs (adriamycin, cyclophosphamide, vincristine, or in polychemotherapy),[4] thermal injury, contact exposure to elemental iron, angiotensin receptor blockage, use of nail hardener, and hyperbilirubinemia. Pseudomonas infection has been reported to cause green chromonychia,[5] and AIDS may also cause a change in color significant being with CD4 counts below 200/cu.mm.[6] Connective tissue diseases such as lupus have also been described in this context. However, KD remains the only vasculitic illness causing this characteristic reddish/orange–brown change in color now being described universally[7] with increasing frequency.

The colored lines start appearing usually around the 5th–8th day of illness,[3] although 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 coloration stays unchanged over the next 7–10 days. Better appreciated in the fingers [Figures 1-3] than the toes [Figure 4], they start disappearing by the end of the 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.

The exact pathogenic mechanism remains unclear. Capillaroscopy has revealed alteration in nailfold capillaries as a consequence of vasculitis, and it has been proposed that the coloration is due to dense band of microscopic splinter hemorrhages, followed by residual pigmentation as demonstrated by dermoscopy.[8]

How to cite this article: Pal P, Roy M, Nandi A, Ahmed N. Orange–brown chromonychia, a novel finding in Kawasaki disease: 10 years since the first publication. Indian J Paediatr Dermatol 2020;21:161-3.

Submitted: 07-Feb-2020
Revised: 21-Feb-2020
Accepted: 29-Feb-2020
Published: 30-Jun-2020

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Access this article online

Website: www.ijpd.in

DOI: 10.4103/ijpd.IJPD_19_20

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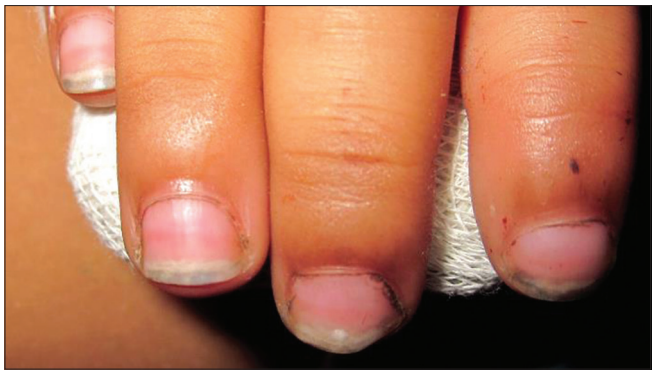

Figure 1: Reddish pink chromonychia of the fingers

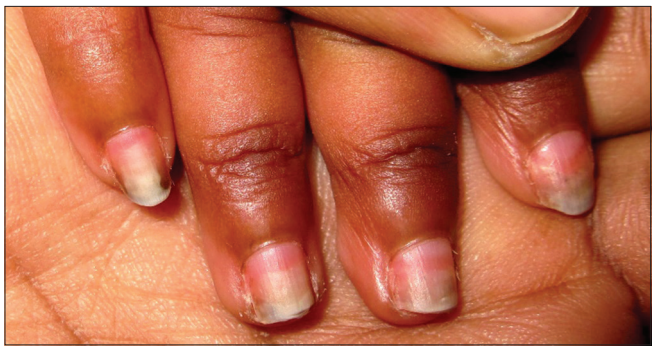

Figure 3: Chromonychia of fingers of some duration

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 presence of periungual desquamation in the fingers and toes, which start around the end of the 2nd week. Although a consistent sign,but because of the late appearance in the subacute phase its clinical utility lies in making a retrospective diagnosis. Another well described albeit a bit rare sign are the transverse grooves (Beau's lines) on the nails which may appear as late as 1–2 months after the disease onset. Beau's lines are better felt than visually appreciated.

Few case reports describe some inconsistent nail changes following KD. Onycholysis has been reported in some cases. Ciastko reported onychomadesis (spontaneous separation of the nail from the matrix) of all twenty nails in an 8-year-old boy with KD, which started 1 week after periungual desquamation.[9] Spontaneously resolving pincer nail deformity (transverse curling of the nail along its longitudinal axis)[10] in an infant with KD and leukonychia partialis[11] (abnormally white proximal portion of the nail) have also been reported. However, all these nail abnormalities are nonspecific, maybe associated with other systemic triggers, and generally resolve spontaneously within 1–2 months.

Since the 2012 publication in rheumatology international, orange/red chromonychia has consistently been described globally. Majority are case reports from countries as

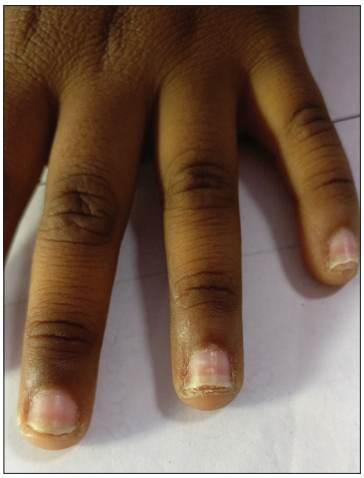

Figure 2: Chromonychia of fingers

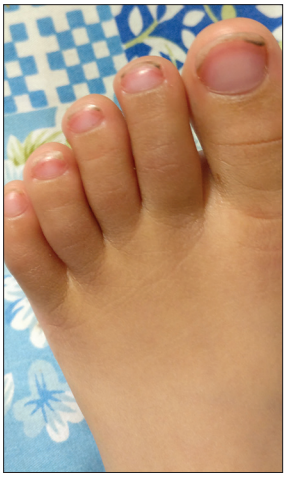

Figure 4: Chromonychia of toes

diverse as the USA, Korea, Australia, Japan, Mexico, and India.[12-14] Authors have described this sign as a novel association and suggested it be considered as an additional clinical sign and a reference[15] in the diagnosis of KD, based on its appearance in the acute phase.

In the recently concluded 12th International KD Symposium at Yokohama, Japan, Pal *et al*.[16] concluded that orange–brown chromonychia is a common clinical finding in KD being present in 63% of the 176 patients admitted between 2012 and 2017 and also the most specific and consistent nail change present in acute KD. They also tried evaluating it for any correlation with coronary artery disease, but no such correlation could be established.

There is an ongoing global search for a specific and consistent biomarker for the early and unambiguous diagnosis of KD. Till that quest is successful, it will be prudent to include this universally described common persistent acute-phase clinical sign as an accessory criteria to aid in diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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A comparison of serum IL6 and CRP levels with respect to coronary changes and treatment response in Kawasaki disease patients: a prospective study

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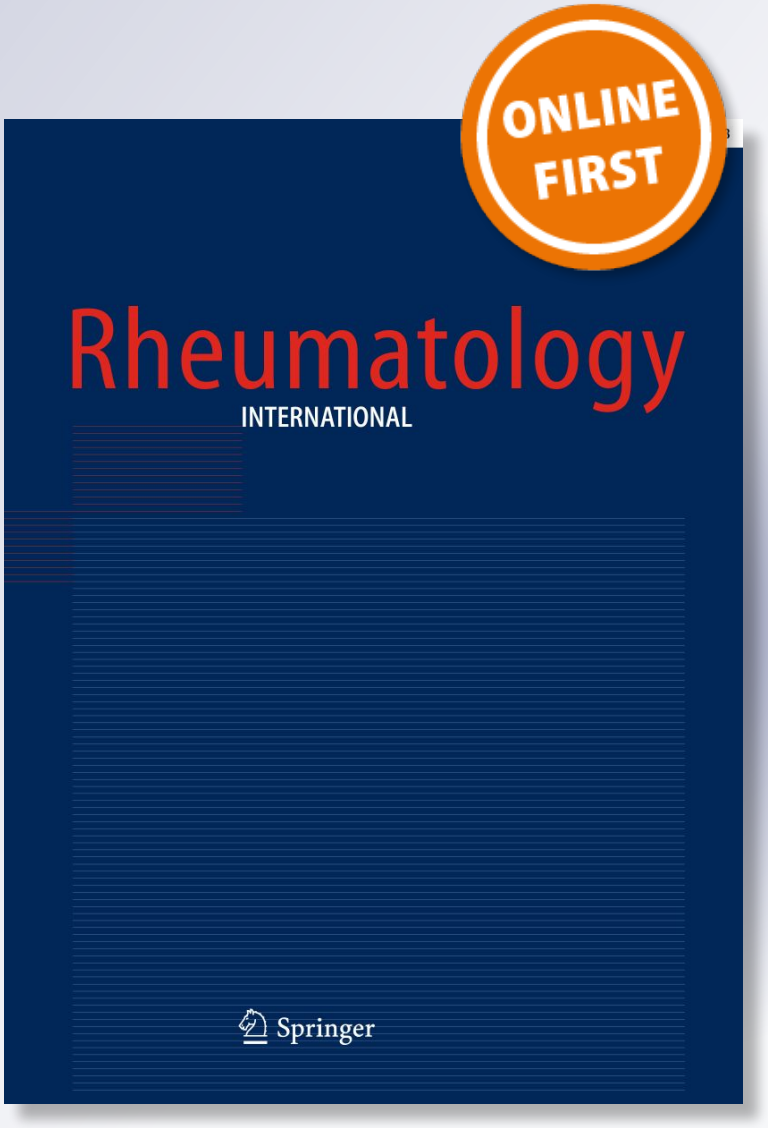
Rheumatology International
Clinical and Experimental Investigations

ISSN 0172-8172

Rheumatol Int
DOI 10.1007/s00296-019-04375-9



Springer

Rheumatology International
https://doi.org/10.1007/s00296-019-04375-9

Rheumatology
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A comparison of serum IL6 and CRP levels with respect to coronary changes and treatment response in Kawasaki disease patients: a prospective study

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Received: 13 May 2019 / Accepted: 7 July 2019

Abstract

To evaluate serum levels of IL6 in patients with Kawasaki disease and compare it with CRP, and to assess the role of these biomarkers in predicting coronary changes and resistance to the first-line therapy of this disease in a subset of Indian population. A single centre prospective observational study was conducted amongst all Kawasaki disease patients for a period of 18 months from January 2017 at Institute of Child Health, Kolkata. Serum IL6 and CRP were compared at diagnosis and after 48 h of administering IVIG in patients who developed coronary changes with those who did not and also among the responders and non-responders to IVIG, the first-line therapy given to these patients. Out of total 72 patients of KD [mean age of presentation: 24 months, M:F = 1.22:1], 30% ($n = 22$) had coronary artery involvement (CALs), and 15% ($n = 11$) were IVIG non-responders. Mean IL6 prior to IVIG in those with CALs was 143.60 pg/ml, which was about three times higher than in those without CALs (mean = 52.90 pg/ml), the difference being significant ($p < 0.01$). Mean CRP values also were significantly raised in patients with CALs ($p < 0.01$) whereas post-IVIG levels of mean serum IL6 was found to be 108.15 pg/ml in non-responders which was about 17 times raised than that in the responders (mean IL6 = 6.22),the difference again was statistically significant ($p < 0.001$).Also, ROC analysis revealed a sensitivity and specificity of 81.0% and 82.0%, respectively, for IL6; 72% and 74%, respectively, for CRP for predicting CALs. This study also shows a sensitivity of 72% and specificity of 68% for IL6 in predicting IVIG resistance whereas that of CRP being 90% sensitive and 36% specific. These results suggest that higher levels of IL-6 and CRP at diagnosis are associated with occurrence of CALs and IVIG resistance in KD patients. Using the cutoff for IL6 and CRP from our study, chances of developing CALs and IVIG resistance can be predicted, which might prevent the development of future complications like aneurysms in such patients.

Keywords Kawasaki disease · Interleukin 6 · C-reactive protein · IVIG resistance

Introduction

Kawasaki disease is a febrile vasculitis affecting mainly the young children, characterised by a constellation of symptoms that has special predilection for the coronaries [1]. Since its first description by Dr. Tomisaku Kawasaki back in 1967, despite extensive research, the aetiology of KD remains enigmatic till date [1, 2]. Multiple postulates regarding the etiopathogenesis have been suggested time and again, one of them being the abnormal activation of the immune system and secretion of cytokines [3]. Interleukin 6 is one such inflammatory cytokine produced in response to activation of monocytes and macrophages in the acute phase of KD, on which studies are lacking from our country [4]. This is a proinflammatory cytokine that incites other inflammatory markers, C-reactive protein being one of them.

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Published online: 13 July 2019

The inflammatory changes that result in coronary arteriopathy occur in a step-by-step fashion as described by necrotizing arteritis, subacute/chronic vasculitis and finally luminal myofibroblastic proliferation (LMP), producing a spectrum of coronary changes ranging from mild, reversible dilations to severe stenosis and giant aneurysms [5]. Various studies have been done from different countries to predict the risk factors for occurrences of these coronary artery lesions(CALs) which led to the formulation of many scoring systems comprising of different parameters like age, serum albumin, sodium, CRP, etc., but none of them apply universally [6].

It was also seen that around 17% KD patients did not respond to the first dose of IVIG and various predictors of resistance, hence, have been suggested and incorporated into the scoring systems [7]. Due to lack of universal acceptance of any one of these scoring systems, prediction of resistant KD cases becomes more difficult. Thus, we need to investigate new novel markers which might help us predict resistance and probability of developing CALs with more accuracy. Hence, we studied the pattern of IL6 in relation to the coronary changes and treatment responses, which may help us in predicting prognosis and targeting new treatment strategies.

Methods

This is a prospective observational study conducted at Institute of Child Health, Kolkata, a tertiary referral hospital in eastern India. Children admitted between January 2017 and June 2018 with complete, incomplete and atypical KD were included and followed up from a period of 1 to 18 months after their discharge depending on time of the disease onset and study period, in the rheumatology OPD of our Institute. Complete, incomplete and atypical KD were diagnosed by fulfilling the classification criteria defined by the AHA 2004 guidelines, and subsequently, by the AHA 2017 guidelines [5]. Paired venous blood samples for interleukin 6 (IL6) and C-reactive protein (CRP) together with other necessary investigations, were drawn and evaluated at the biochemistry department at diagnosis and 48 h after administering IVIG. The serum concentrations of CRP were quantitatively determined by particle-enhanced turbidimetry on the Roche Integra 400 Plus© biochemistry analyzer. Linearity was till 200 mg/L. Biological reference interval was < 5 mg/L and serum IL6 was measured on the Roche cobas e411© immunoassay analyser with a linearity till 5000 pg/ml and biological reference interval of < 7 pg/ml.

2D Echocardiography was done at diagnosis, after 2 weeks of IVIG and at 6-week follow-up by an experienced paediatric cardiologist at our Institute. The coronary artery lesions (CALs) and positive echocardiography findings for diagnosis of incomplete KD, as defined by the AHA 2004, and subsequently 2017 guidelines, were followed [5]. Patients, who had CALs at diagnosis, were followed up with echocardiography every 3–5 days to review for any evidence of further progression.

The responder group included patients who received a single dose of IVIG (2 g/kg) treatment and had no reappearance of fever 48 h after IVIG, while the non-responder group included patients who had persistent or recrudescent fever after 48 h of IVIG and needed a second dose of IVIG or Infliximab [6].

Ethics statement

Data were collected and given for analysis to a competent biostatistician. For statistical analysis, SPSS 24.0 © software was used. Normality of data was checked before applying parametric tests. Data had been summarised as mean and standard deviation for numerical variables and counts for discrete data and percentages for categorical variables. *t* tests were used for a difference in mean involving independent samples or unpaired samples. Unpaired categorical data were compared by Chi-square test or Fischer's exact test, as appropriate.

Receiver operating characteristic (ROC) curves were derived from the pre-IVIG serum CRP and IL6 levels in all KD patients. In the ROC curve, the sensitivity and specificity, for the prediction of CALs and IVIG resistance in the KD patients were calculated by combining the optimal cutoff values for each cytokine using the Youden index. The difference was considered significant at P values less than 0.05. All data analyses were performed using SPSS© version 24.0 software.

This study was approved by the Institutional Ethics Committee (IEC) (IEC Regn No. ECR/359/Inst/WB/2013) of Institute of Child Health, Kolkata in November 2016 (Ethical clearance protocol no. IEC/107a/2016 vide letter ICH/33/2016 dated 29th Nov 2016).

Results

74 patients were diagnosed with KD during this period of 18 months. 2 were excluded as they did not consent and 72 patients were finally recruited. Among the study population, 31(43.1%) patients were female and 41(56.9%) were male with a M:F ratio of 1.22:1, 79.2% belonged to the age group 1–5 years. Median age was 19 months with Interquartile range (IQR) of 13.75–30.5 months. Seasonality was observed in disease occurrence with maximum incidence in the months of April and May (15% of admissions) and

lowest in October–November. The mean duration fever at presentation (mean ± S.D.) was 8.9167 ± 2.8222 days.

83% patients were diagnosed as complete KD and 17% were diagnosed as incomplete KD. 22 (30.6%) patients had coronary artery involvement. The most common artery to be involved was the LAD followed by RCA. Majority had small aneurysms (*z* score between 2.5 and 5); however, two (2.7%) had giant aneurysms involving the LAD. In the echocardiography follow-up at 2 weeks, it was seen that the giant aneurysms increased in size as measured by *z* scores and three patients who had small/medium aneurysms previously still had a *z* score > 2.5 but in decreasing trend and rest all had normal *z* scores (< 2) by 2 weeks. At 6 weeks, none had increasing *z* scores, patients with giant aneurysms (also received Infliximab) had decreased scores compared to the earlier one and rest all had normal *z* scores (< 2).

Regarding the treatment outcomes, 61(84.7%) patients responded to the first dose of IVIG characterised by defervescence. 11(15.3%), however, did not respond to first dose IVIG and were given second-line therapy with Infliximab.

Demographic parameters like age, sex or differences in the mean duration of fever were not statistically significant among responders and non-responders. All non-responders had coronary artery involvement.

The difference between the mean pre-IVIG CRP in the responders and non-responders was not statistically significant ($p = 0.1973$), although the mean post-IVIG CRP of non-responders was significantly higher ($p < 0.0001$), compared to responders. Similarly, mean pre-IVIG IL6 was also not found to be significantly different in responders and non-responders ($p = 0.2242$). But the mean post-IVIG IL6 was significantly higher in non-responders ($p < 0.0001$) (Table 1).

We compared both these levels in pre- and post-IVIG sera with coronary involvement and found that mean pre-IVIG CRP and IL6 in patients without any coronary artery involvement were significantly ($p < 0.0001$) less compared to patients with CALs (Table 2).

We also performed ROC curve analysis for pre-IVIG CRP and IL6 in predicting CALs and IVIG resistance and using Youden index, optimal cutoff for CRP was 40 mg/L with a sensitivity of 90%, specificity of 36.0% and area under the curve of 0.624 (95% CI 0.50–0.73) for predicting IVIG resistance (Fig. 1), and pre-IVIG serum IL6 had a sensitivity of 72% and specificity of 68% with area under the curve of 0.702 (95% CI 0.58–0.80) for predicting IVIG resistance at > 75 pg/ml cutoff value (Fig. 1) (Table 3).

For predicting CALs, pre-treatment IL6 had a sensitivity of 81.0% and specificity of 82.0% at the cutoff value of > 75 pg/ml (area under the curve 0.788, 95% CI 0.67–0.87) (Fig. 1), whereas pre-IVIG serum CRP had a sensitivity of 72.0% and specificity of 74% at 78 mg/L cutoff value (area under the curve 0.87, 95% CI 0.77–0.93) (Fig. 1)(Table 3).

Limitations of the study

1. Small sample size.
2. IL-6 estimation is relatively expensive.

Table 1 Serum CRP and IL6 levels pre- and post-IVIG in patients with Kawasaki disease who were IVIG responders and non responders

Pre IVIG				Post IVIG		
CRP/IL6 levels	Non responder ($n = 11$)	Responder ($n = 61$)	p value**	Non responder ($n = 11$)	Responder ($n = 61$)	p value**
CRP	107.03 (90.50)	76.06 (68.04)	> 0.05	86.70 (30.01)	15.00 (15.13)	< 0.01
IL6	106.06 (67.01)	66.03 (75.97)	> 0.05	108.15 (51.43)	6.22 (15.86)	< 0.01

Values are the mean (S.D.) mg/dl (CRP) and pg/ml (IL6). *IVIG* intravenous immunoglobulin, *CRP* C Reactive Protein, *IL-6* interleukin-6

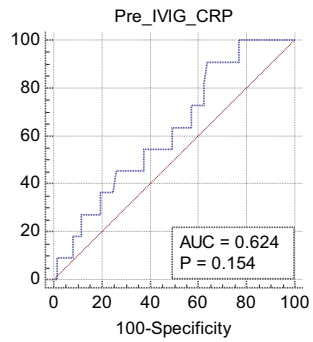
** p value < 0.05 is taken as significant

Table 2 Serum CRP and IL6 levels pre- and post-IVIG in patients with Kawasaki disease in whom CALs were absent and those in whom CALS were present during the disease process

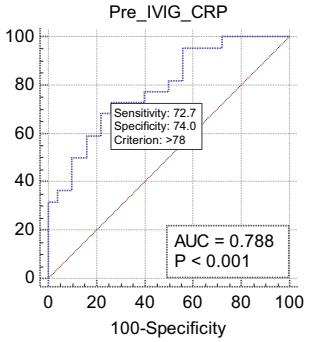
Pre IVIG			Post IVIG		
CRP/IL6 Levels	Without CALs ($n = 50$)	With CALs ($n = 22$)	Without CALs ($n = 50$)	With CALs ($n = 22$)	p value**
CRP	57.36 (40.46)	135.17 (96.53)	12.40 (12.71)	56.77 (39.43)	< 0.001
IL6	52.90 (36.46)	143.60 (99.72)	3.32 (4.50)	63.78 (62.31)	< 0.001

Values are the mean (S.D.) mg/dl (CRP) and pg/ml (IL6). *IVIG* intravenous immunoglobulin, *CALs* coronary artery lesions, *IL-6* interleukin-6, *CRP* C Reactive Protein

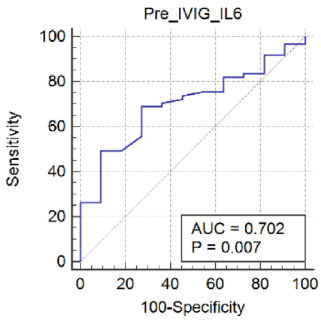
** p value < 0.05 is taken as significant



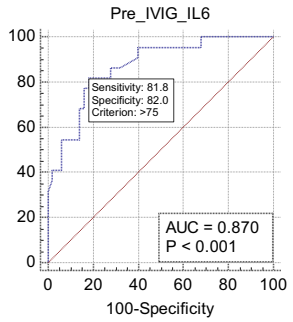
Pre IVIG-CRP in predicting resistance to IVIG



Pre IVIG-CRP in predicting CALs



Pre IVIG-IL6 in predicting resistance to IVIG



Pre IVIG-IL6 in predicting CALs

Fig. 1 ROC analysis for predicting IVIG resistance and CALs

Table 3 Sensitivity and specificity of CRP and IL6 levels pre-IVIG for predicting IVIG resistance and Coronary artery lesions (CALs) in patients with Kawasaki disease

Pre IVIG CRP/IL6 (Cut off)	Sensitivity %	Specificity %
IVIG resistance~		
CRP (40 mg/dl)	90	36
IL6 (75 pg/ml)	72	68
CALs~		
CRP (78 mg/dl)	72	74
IL6 (75 mg/dl)	81	82

IVIG intravenous immunoglobulin, *CRP* C Reactive Protein, *IL-6* interleukin-6

Discussion

IL-6 is a pleotropic cytokine that is produced by a variety of cells and acts on a wide range of tissues exerting a growth inducing, growth inhibitory and differentiation-inducing effects depending on the nature of the target cells. IL-6 leads to B cell differentiation, induction of acute-phase proteins in the liver cells like CRP and various growth promoting as well as inhibiting effects on the hematopoietic stem cells and malignant cells [7]. Hence, IL-6 may play a role in the pathogenesis of many autoimmune diseases, plasma cell neoplasia and glomerulonephritis [8]. Kawasaki disease, as suggested by various researchers, is a condition characterised by dysregulated inflammation in the blood vessels as evident from the high levels of CRP, and ESR found in the acute phase. Previous studies on IL-6 in patients of Kawasaki disease have showed elevated levels of serum IL-6 in all patients in acute phase of KD and lower levels in subacute phase [9], and there was a significant difference in the levels between those with and without coronary artery aneurysms during the first week [10].

Studies also have found that there were no significant differences between the responders and non-responders with

regard to age, gender and fever duration before treatment; however, significant difference has been demonstrated in the levels of markers like CRP, IL6, IL18, pro BNP, etc., in the sera of KD patients [11].

The present study was done to compare IL6 with well-known marker, CRP and how it changes with the disease severity as seen in the form of CALs and resistance to IVIG in the Indian population. Our results showed significantly higher levels of these markers in patients who later developed CALs and also in the non-responders, in contrary to those who did not have CALs or resistance to IVIG. We also compared demographic factors like age, sex and duration of fever and did not find any significant relation with development of CALs or disease refractoriness.

Another previous study on cytokines and Kawasaki disease showed that prior to treatment with IVIG, the level of IL-6 among other cytokines was slightly lower in IVIG non-responders compared to IVIG responders, but post-IVIG, the IL-6 levels were significantly higher in IVIG non-responders than in IVIG responders; thus, suggesting that a slower decrease in IL-6 levels after treatment with IVIG may be related to IVIG resistance and the occurrence of CALs in these KD patients and the attenuation of proinflammatory cytokine responses, especially IL-6, following infusions of IVIG may play an integral role in the rapid resolution of symptoms and in reduced levels of acute-phase proteins in children with KD [12]. In our study population, we found similar results.

We tried to find optimum cutoff values for CRP and IL6 prior to the treatment with IVIG in predicting CALs and IVIG resistance in Indian population and found that pre-IVIG serum CRP had a sensitivity of 90% and specificity of 36.0% for predicting IVIG resistance at cutoff value of 40 mg/L but pre-IVIG serum IL6 had a sensitivity of 72% and specificity of 68% for predicting IVIG resistance at > 75 pg/ml cutoff value which shows better accuracy of IL6 in predicting IVIG resistance than CRP.

For predicting CALs, on the other hand, pre-treatment IL6 had a sensitivity of 81.0% and specificity of 82.0% when the cutoff value was > 75 pg/ml whereas pre-IVIG serum CRP had a sensitivity of 72.0% and specificity of 74% at 78 mg/L cutoff value.

Hence, it can be suggested from the present study that an acute-phase serum IL6 level of > 75 pg/ml is associated with higher likelihood of developing coronary changes and IVIG resistance in our population subset. Furthermore, it showed a better predictability than CRP.

Hence, to conclude, the present study shows that significantly higher serum IL6 and CRP levels are associated with CALs and resistance to IVIG. Serum IL6, therefore, can be used as a new novel marker for prediction of coronary artery involvement and resistance to IVIG.

Funding None.

Compliance with ethical standards

Conflict of interest The above authors Dr. Alolika Nandi, Dr. Priyankar Pal and Dr. Surupa Basu declare that there is no conflict of interest.

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Clinical Rheumatology
https://doi.org/10.1007/s10067-022-06344-3

ORIGINAL ARTICLE

Risk factors in IVIG-resistant Kawasaki disease and correlation with Japanese scoring systems — a study from Eastern India

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Received: 22 May 2022 / Revised: 10 August 2022 / Accepted: 18 August 2022

Abstract

Objectives To assess the risk factors of intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (KD) and to evaluate the performance of the three Japanese risk-scoring systems, namely the Kobayashi, Egami, and Sano scores in predicting IVIG resistance among the Indian patients.

Methods Prospective observational study on children admitted with KD at Institute of Child Health, Kolkata, over a period of 16 months, from January 2019 to April 2020. The study included 70 KD patients all of whom were treated with IVIG. Clinical parameters, laboratory variables, and risk scores were compared between the IVIG-responsive and the IVIG-resistant groups.

Results A total of 31.4% were IVIG non-responders. Skin rash was found to be significantly associated with IVIG-resistant KD. The IVIG-resistant group had higher total bilirubin, lower albumin, higher CRP levels, and higher ALT and AST levels. High Kobayashi score, high Egami score, and high Sano score were significantly associated with IVIG resistance, individually. Sano score had the highest sensitivity (81.8%) and Kobayashi score had the highest specificity (77.1%) in our cohort.

Conclusion The presence of skin rash, high total bilirubin, high CRP, high AST, high ALT, and low albumin were important predictors of IVIG resistance in our population. Among the three scores, Sano score is the most reliable in identifying potential non-responders to IVIG. But Sano score lacked good specificity. Therefore, Indian KD patients may need an exclusive scoring system to predict non-responsiveness to IVIG so that a more aggressive therapy can be instituted at the earliest.

Key points
- *Early prediction of IVIG-resistant KD is necessary to limit cardiac injuries.*
- *Sano score has high sensitivity to predict IVIG resistance in Indian population.*

Keywords IVIG resistance · Japanese risk scores · Kawasaki disease

Introduction

Kawasaki disease (KD), an acute-onset systemic vasculitis, is steadily becoming the most common form of medium-sized primary vasculitis. KD particularly affects the coronary arteries, causing coronary artery aneurysms (CAA) in 15–25% of untreated patients while 2–3% of untreated cases die as a result of coronary vasculitis [1]. In view of the frequency and severity of coronary artery complications, there has been increasing interest in treatments to reduce the risk of CAA [2]. Administration of intravenous immunoglobulin (IVIG) lowers the prevalence of CAA to less than 5% [2]. However, 10–15% of KD patients show persistent fever despite treatment with high-dose IVIG (2 g/kg), a condition known as IVIG-resistant KD [3]. As the incidence of KD has increased, cases of IVIG-resistant KD have also increased [4]. It has been seen that children with IVIG resistance are more prone to develop cardiac injury [5, 6]. Therefore, early identification and appropriate treatment of resistant KD are of utmost importance to prevent cardiac damage. Recent research has focused on identification of predictors of IVIG resistance and several risk scoring algorithms have been developed [5,

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7]. In Japan, the Sano, Kobayashi, and Egami risk scores [7, 8] are commonly used. However, the performance of these scores was not satisfactory when applied to children with KD outside Japan. Different countries and ethnic groups will therefore need different models to predict IVIG-resistant KD.

The purpose of this study is to determine the variables associated with IVIG resistance and also to assess the performance of the three Japanese risk-scoring systems, developed to predict IVIG resistance, when applied to the Indian population.

Methods

Study design

This single-centre prospective observational study analyzed a series of patients who fulfilled the criteria for KD admitted at the pediatric ward of Institute of Child Health, Kolkata, India, from January 2019 to April 2020. The criteria for the diagnosis of complete KD followed the Japanese criteria (5th revision of the diagnostic guideline for KD). Patients having significant structural cardiac defect not related to KD or having insufficient laboratory data to perform the Kobayashi, Egami, and Sano scores were excluded.

All patients were treated with 2 g/kg of IVIG along with aspirin (30 mg/kg/day) at the acute phase of KD. Patients were classified into two groups:

(1) IVIG-resistant group (defined as those patients who had persistence or recurrence of fever 36 h after the end of initial IVIG infusion)
(2) IVIG-responsive group (defined as those patients who became afebrile after receiving a single dose of IVIG treatment).

Written informed consent was taken from the parents of the study subjects.

Demographic data of age, sex, and duration of fever before IVIG administration as well as clinical features like conjunctival injection, skin rash, mucosal changes, extremity changes, lymphadenopathy, perianal excoriation, and BCG scar reactivation were noted.

Laboratory parameters like total white cell count, neutrophil percentage, lymphocyte percentage, hemoglobin level, platelet count, sodium level, ALT, AST, total bilirubin, albumin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were noted. Echocardiography was done at diagnosis. The Kobayashi, Egami, and Sano scores were individually calculated for all the study subjects.

Ethics

The study was approved by the Institutional Ethics Committee of Institute of Child Health, Kolkata (IEC/172/2018).

Statistical analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample *t*-tests for a difference in mean involved independent samples or unpaired samples. Unpaired proportions were compared by chi-square test or Fisher's exact test, as appropriate. p-value ≤ 0.05 was considered statistically significant.

Results

A total of 71 children were admitted with KD during the 16-month study period, but 1 was excluded due to the presence of moderate VSD. In the final group with 70 patients, 48 (i.e., 68.6%) responded to IVIG (IVIG-responsive group) and 22 (i.e., 31.4%) did not respond to IVIG (IVIG-resistant group). In majority of the responsive cases, defervescence was achieved within 12–24 h except one whose fever subsided after 30 h of IVIG infusion. All resistant cases were given infliximab (IFX) at 5 mg/kg. Of the 22 IVIG-resistant patients, 20 became afebrile within 24 h of IFX administration and remaining 2 within 48 h. However, these findings were not analyzed any further.

In IVIG-resistant group, 13 (59.1%) patients had complete KD and 9 (40.9%) patients had incomplete KD. In both the groups, majority of patients belonged to the age group of 13–60 months (68.2% and 68.8% respectively). There was no significant correlation between IVIG resistance and age, gender, or duration of fever before IVIG treatment.

No significant differences were found between IVIG-responsive and IVIG-resistant groups based on clinical features like conjunctival injection, mucosal changes, extremity changes, lymphadenopathy, perianal excoriation, and BCG scar reactivation (p values non-significant). Interestingly though, skin rash was found to be significantly associated with IVIG-resistant KD (86.4% vs 62.5%; p value = 0.04) (Table 1).

Among the laboratory parameters, the two groups were statistically similar with respect to total counts, neutrophil percentage, lymphocyte percentage, hemoglobin level, platelet count, sodium level, and ESR. However, there was a significant correlation between liver enzymes and IVIG

Table 1 Comparison of clinical features between IVIG-resistant and IVIG-responsive groups

Clinical features	IVIG-resistant group	IVIG-responsive group	*p* value	Comment
Mean duration of fever before IVIG administration(days)	6.04	7.21	0.07	Non-significant
Conjunctivitis	17 (77.3%)	36 (75.0%)	0.84	Non-significant
Mucosal changes	19 (86.4%)	42(87.5%)	0.89	Non-significant
Skin rash	19 (86.4%)	30 (62.5%)	**0.04***	**Significant**
Extremity changes	12 (54.5%)	29 (60.4%)	0.64	Non-significant
Lymphadenopathy	12 (52.2%)	29 (61.7%)	0.32	Non-significant
Perianal excoriation	5 (22.7%)	20 (41.7%)	0.12	Non-significantNon-significant
BCG scar reactivation	4 (18.2%)	6 (12.5%)	0.53	Non-significant

The symbol * signifies the *p* values which are statistically significant

resistance. The mean ALT (mean ± s.d.) of patients in IVIG-resistant group was 97 ± 87.9 and in IVIG-responsive group, the value came as 62 ± 47.9. The mean AST (mean ± s.d.) of patients was 105 ± 140.07 and 41 ± 22.74 in IVIG-resistant group and IVIG-responsive group respectively. Thus, ALT and AST levels were significantly higher ($p = 0.04$, $p = 0.003$ respectively) in patients with resistant KD. It was also found that compared with IVIG-responsive group, the resistant group had higher total bilirubin (1.34 ± 1.01 vs 1 ± 0.41; *p* value = 0.04), lower albumin (2.9 ± 0.04 vs 3.2 ± 0.32; *p* value = 0.002), and higher CRP levels (136 ± 105.94 vs 121 ± 85.06; *p* value = 0.002).

Out of the 22 IVIG-resistant patients, 14 (63.6%) patients had high Kobayashi score (≥ 4), 15 (68.2%) had high (3–5) Egami score, and 18 (81.8%) had high Sano scores (> 2). So, there was a significant association between IVIG resistance and high Kobayashi, Egami, and Sano scores individually (*p* value = 0.0009; *p* value = 0.01; *p* value = 0.026 respectively). The sensitivity and specificity of Kobayashi score for predicting IVIG resistance were 63.6% and 77.1% respectively (Fig. 1). Positive predictive value was 56.0, negative predictive value was 82.2, and accuracy was 72.8. The sensitivity and specificity of Egami score was 68.2% and 64.6% respectively. Positive predictive value was 46.9, negative predictive value was 81.6, and accuracy was 65.7. The sensitivity and specificity of Sano score came as 81.8% and 45.8% respectively. Positive predictive value was 40.9, negative predictive value was 84.6, and accuracy was 57.0.

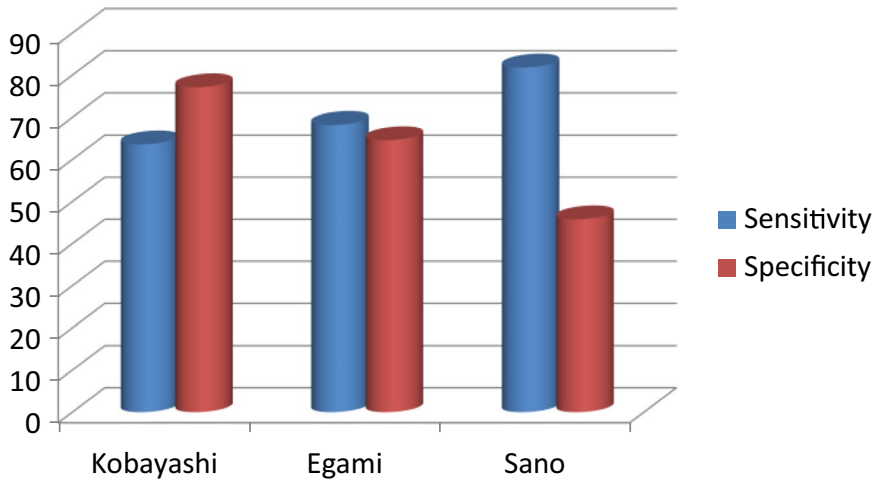

Fig. 1 Comparison of items evaluated in the three risk scores

Score	Sensitivity	Specificity
Kobayashi	63.6%	77.1%
Egami	68.2%	64.6%
Sano	81.8%	45.8%

Discussion

Early identification of IVIG resistance is critical to initiate more effective therapies aimed to limit serious cardiac complications, especially coronary dilatations and aneurysms. This study has focused on recognizing early predictors of IVIG resistance by comparing demographic, clinical, and laboratory parameters between IVIG-responsive and -resistant groups.

Among demographic parameters, we had compared age, gender, and fever duration, none of which was found to be significantly associated with IVIG resistance. This was in stark contrast to previous studies that had established male sex as an independent risk factor [9–11] and also contradicted the findings of Do YS et al. [12] who had demonstrated the febrile period to be significantly longer in the resistant group. According to previous studies, IVIG-resistant cases tend to be younger with peak incidence occurring below 6 months of age [13]. However, there was no significant correlation between IVIG resistance and age in this study. The reason for such differences could be due to the small size of our study group which was not sufficient to demonstrate any difference in demographic pattern. Among clinical features, polymorphous rash has been identified as a risk factor for IVIG resistance, a finding similar to previous studies by [14, 15].

Raised inflammatory markers, hepatic dysfunction, and their association with IVIG resistance have been described before [6, 9, 10, 14, 16–18]. In this study too, high CRP and liver enzymes were found to be strongly associated with IVIG resistance (Table 2). Also, the resistant group was found to have higher bilirubin and lower albumin levels. Raised liver enzymes and high bilirubin may suggest more severe systemic inflammation and vasculitis in liver in resistant cases. Inflammatory cell infiltration in hepatic sinusoids and portal areas and Kupffer cell proliferation have been described in previous literature [19, 20]. Lower albumin levels have been associated with resistant KD and may reflect higher degrees of inflammation and vascular leakage [21–24].

It has been well established that high neutrophil percentage and low sodium levels are predictors of IVIG resistance [14, 16]. The association between low platelet count and IVIG resistance has also been demonstrated before [6, 9, 14, 25]. In contrast, the two groups in our study were similar with respect to total counts, neutrophil percentage, lymphocyte percentage, hemoglobin level, platelet count, sodium level, and ESR. Therefore, it can be inferred that the risk factors for IVIG resistance seem to vary between different countries and ethnic groups. The reasons for such a difference could be due to genetic difference or some other environmental factors and need to be investigated further.

In the Japanese population, the sensitivity and specificity of all the three risk scores were moderate to high (Kobayashi: sensitivity 86%, specificity 67%; Egami: sensitivity 78%, specificity 76%; Sano: sensitivity 77%, specificity 86%) [22, 26, 27]. However, these scores were found to have limited predictive value for IVIG responsiveness in other countries as confirmed by previous studies in North America [11], UK [28], China [15, 29], Italy [30], and Iran [31]. Similar studies carried out in the Korean [17] and German [32] children with KD reported that the Japanese risk-scoring systems had low sensitivity for predicting IVIG resistance. Therefore, the formulation of separate and specific scoring systems for individual countries and ethnic groups is necessary.

In our study, among the three scores, Kobayashi score had the highest specificity (77.1%). However, our main aim being early identification of high-risk patients, high sensitivity of scoring system is essential. Kobayashi score and Egami score lacked good sensitivity (63.6% and 68.6% respectively) whereas Sano score had the highest sensitivity (81.8%) (Fig. 2). Therefore, it can be concluded that among the three scores, Sano score may be the most reliable scoring system when applied to Indian population.

Table 2 Comparison of laboratory parameters between IVIG-resistant and IVIG-responsive groups

Laboratory values	IVIG-resistant group	IVIG-responsive group	*p* value	Comment
Mean total counts (mm3)	16,644	18,189	0.38	Non-significant
Mean neutrophil (%)	72	69	0.34	Non-significant
Mean lymphocyte (%)	24	26	0.39	Non-significant
Mean Hb (gm/dL)	9.8	10	0.57	Non-significant
Mean platelet (lakh/mm^3)	5.6	4.9	0.57	Non-significant
Mean sodium (mmol/L)	131	132	0.28	Non-significant
Mean ALT (IU/L)	97	63	**0.04***	Significant
Mean AST (IU/L)	105	41	**0.003***	Significant
Mean total bilirubin (mg/dL)	1.34	1	**0.04***	Significant
Mean albumin (g/dL)	2.9	3.2	**0.002***	Significant
Mean CRP(mg/dL)	136	121	**0.002***	Significant
Mean ESR (mm/h)	79	75	0.57	Non -Significant

The symbol * signifies the *p* values which are statistically significant

Fig. 2 Comparison of sensitivity and specificity of Kobayashi, Egami and Sano scores

Items	Egami score	Kobayashi score	Sano score
CRP	•	•	•
Age	•	•	
Days of illness	•	•	
ALT	•		
Total bilirubin			•
AST		•	•
Sodium		•	
Neutrophil(%)		•	
Platelet count	•	•	

The only drawback is that the specificity of Sano score was low (45.8%). The accurate prediction of potentially IVIG-resistant patients still remains a challenge.

This study had several limitations: (1) The sample size was small. (2) The study was conducted in a single center. (3) The study was carried out in a tertiary medical center, so hospital bias cannot be ruled out.

In conclusion, the results of our analyses have shown a correlation between IVIG resistance and presence of skin rash, high total bilirubin, high CRP, high AST, high ALT, and low albumin. Therefore, these parameters can serve as predictors of IVIG resistance and alert clinicians to implement necessary therapeutic approach. Our study has also revealed a significant association between IVIG resistance and high Kobayashi, Egami, and Sano scores. Among the three scores, Sano score had the highest sensitivity and negative predictive value and thus may be considered a useful score in identifying potential IVIG-resistant KD patients. However, Sano score lacked good specificity. Therefore, formulation of an exclusive scoring system for the Indian population is the need of the hour and similar studies focusing on this matter should be encouraged.

Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Disclosures None.

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Macrophage Activation Syndrome in Kawasaki Disease

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Received: June 21, 2013;
Initial review: July 01, 2013;
Accepted: December 27, 2013.

Background: Kawasaki disease is an acute febrile vasculitis of childhood. Macrophage activation syndrome is a rare life threatening complication. **Case characteristics:** 4-year-old boy with Kawasaki Disease treated with intravenous immunoglobulins. **Observation:** He developed encephalopathy, hepatosplenomegaly and pancytopenia. Blood investigations and bone marrow aspiration suggested macrophage activation syndrome. **Outcome:** Good response to pulse methylprednisolone (30 mg/kg/d) for 5 days. **Message:** Macrophage activation syndrome may complicate Kawasaki disease.

Keywords: *Lymphoproliferative disorders, Mucocutaneous lymph node syndrome.*

Macrophage activation syndrome (MAS) occurs secondary to many diseases, including infections, neoplasms, hematological conditions, and rheumatic disorders. It is characterized by persistent fever, pancytopenia, liver dysfunction, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia, elevated serum lactate dehydrogenase, and hypertriglyceridemia [1,2].

CASE REPORT

A 4-year-old boy was admitted with history of high fever for 14 days. He had a history of diffuse maculopapular truncal rash which started on day-4 of fever and persisted for 4 days. There was bilateral non-purulent conjunctivitis from the 3rd to 6th day of fever along with erythema of tongue and lips. Blood counts done elsewhere on day-12 were: hemoglobin 9.6 g/dL, total leukocyte count 18.8 × 10^9/L, platelet count 886 × 10^9/L, Erythrocyte sedimentation rate (ESR) 70 mm in 1st hour, and C-reactive-protein (CRP) 86 mg/L. Widal and Mantoux tests were negative. On examination, he was irritable, and had pedal edema, orange brown chromonychia, right cervical lymphadenopathy and hepatosplenomegaly. Investigations showed serum sodium of 130 mmol/L, Alanine aminotransferase (ALT) of 263 U/L, serum albumin of 2.8 g/dL, and a sterile blood culture. Urine microscopy revealed 10-12 pus cells/ high power field; culture was sterile. Echocardiography showed perivascular brightness with lack of tapering in left anterior descending artery and an aneurysm measuring 5 mm. Aneurysm (4.6 mm) was also present in left main coronary artery. A diagnosis of Kawasaki disease (KD) was made and intravenous immunoglobulins (IVIg) were administered at 2 g/kg over 24 hours.

After being afebrile for 48 hours, fever recurred on day-17. He became drowsy, developed gum bleeding and further increase in size of liver and spleen. Repeat blood counts showed hemoglobin 6.8 g/dL, total leukocyte count 4.6 × 10^9/L, platelet count 16 × 10^9/L, ESR 12 mm in 1st hour and CRP 256 mg/L. ALT increased to 468 U/L, International normalized ratio was 1.8 and activated partial thromboplastin time was 68 seconds. Persistent fever, encephalopathy, hepatosplenomegaly, deteriorating liver function and pancytopenia along with

falling ESR raised the suspicion of MAS. Further blood investigations were: ferritin 15716 ng/dL, fibrinogen 96 mg/dL, triglyceride 463 mg/dL and lactate dehydrogenase 1775 U/L. Bone marrow aspiration documented phagocytosis of hematopoietic cells by well differentiated macrophages that was diagnostic of MAS.

Intravenous pulse methylprednisolone was given at 30 mg/kg/d for 5 days. Fever gradually subsided, blood counts normalized (on day-24), and the child was discharged after 13 days on oral aspirin 5 mg/kg/d. The patient is now clinically well and on regular follow-up. Echocardiography after 6 weeks showed regression of aneurysms.

DISCUSSION

Kawasaki disease is an acute multi system vasculitis of the small and medium-sized arteries with a predilection for coronaries. Our patient had all the clinical features of KD [3-5]. Our patient had a recurrence of fever despite intravenous administration of IVIg, and he deteriorated rapidly after 48 hours. Refractory fever occurs in 10% of patients with KD despite treatment with IVIg; the suggested treatment is intravenous pulse therapy with methylprednisolone or infliximab [6]. Persistent fever following IVIg administration, falling blood counts and ESR, hepatosplenomegaly, and alteration of mental status prompted us to investigate him for MAS.

MAS patients have profoundly depressed natural-killer (NK) cell function. NK cells and cytotoxic T-lymphocytes fail to kill infected cells and thus remove the source of antigenic stimulation leading to persistent antigen-driven activation and proliferation of T-cells associated with persistent production of cytokines, that stimulate macrophages. Cytotoxic dysfunction leads to persistent expansion of T cells and macrophages, and escalating production of proinflammatory cytokines [7-9].

There have been few reported cases of MAS in KD [10-12]. Latino, *et al.* [11] reported that 10 out of the 12 patients with KD in their series met at least 5 of the 8 criteria necessary for diagnosis of MAS. Treatment beyond the standard KD protocol (aspirin + IVIg) was necessary in all but 1 patient. Eight of these patients were also given multiple doses of IVIg. We administered methylprednisolone pulse therapy after single dose of IVIg with dramatic response.

We conclude that MAS may rarely complicate the course of KD; prompt treatment with pulse methylprednisolone may result in favourable outcome .

Acknowledgement: Dr Prabhas Prasun Giri and Dr Md Fekarul Islam.
Contributors: All authors were involved in case management. DM drafted the manuscript that was approved by all authors.
Funding: None; *Competing interests:* None stated.

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CASE REPORT

Multiple Giant Coronary Aneurysms in an Infant with Prolonged Fever

Subhajit Dey Sarkar[1], Priyankar Pal[2], Prabhas P Giri[3], Debadatta Mukhopadhyay[4]

Abstract

Kawasaki disease is a systemic vasculitis, sometimes presenting atypically in infancy, often leading to a late diagnosis, and resulting in devastating consequences. We report a 2-month-old baby presenting with fever of unknown origin. Echo showed giant aneurysms in all three coronary arteries with intraluminal thrombus in one artery that required thrombolysis and anticoagulation.

Keywords: Coronary artery aneurysm, Kawasaki disease, Streptokinase, Thrombolysis.

Pediatric Infectious Disease (2021): 10.5005/jp-journals-10081-1268

Introduction

Kawasaki disease (KD) is an acute onset multisystem vasculitis of undetermined etiology presenting as febrile illness in children mostly younger than 5 years of age. The unique clinical symptom complex of this disease was first described by Dr Tomisaku Kawasaki in 1967.[1] European studies have shown the incidence to be 5–10 per 100,000 children under the age of 5 years, but incidence is higher in Asian countries like Japan, Korea, and Taiwan.[2]

The etiology is largely unknown, but genetic, infectious, and immunological factors possibly play a role.

Kawasaki disease is a clinical diagnosis, but all the clinical features may not be present in the same patient or at the same time thus making diagnosis difficult. It affects small and medium sized vessels with a peculiar predilection for the coronary arteries leading to coronary artery aneurysms (CAA) and thrombosis, occasionally resulting in long-term sequelae like stenosis and myocardial infarction.

The standard treatment of 2 g/kg intravenous immunoglobulin (IVIG) together with aspirin (30–50 mg/kg/day), is effective in reducing fever in 80–90% of patients and decreasing the rate of coronary artery aneurysm formation from 20–25% to 3–5%.[3]

Case Description

A 2-month-old male child presented with high fever for 15 days. Clinical examination of the child was unremarkable. Investigations showed hemoglobin of 7.9 g/dL, total leukocyte count of 24,200 cmm with 78% neutrophils, and platelet count of 7.34 lacs/cmm. Cross reacting protein (CRP) was 158 mg/L. Chest X-ray, cerebrospinal fluid (CSF) study, and blood and urine cultures were negative. Fever persisted even on broad spectrum iv antibiotics and a repeat blood test showed platelet count of 10.2 lacs/mm^3 with a CRP of 212 mg/L. To explore the possibility of KD as a cause for the fever with thrombocytosis, echocardiography was performed which showed multiple giant aneurysms involving all major coronaries: left main-coronary artery (LMCA) proximal part 6.3 mm (*z* score +16.1) and proximal left anterior descending (LAD) artery had a giant aneurysm 10 × 12 mm (with sluggish flow) with clot in LAD 4 × 2 mm in size (Fig. 1). There was a huge distal aneurysm 9.2 × 8.4 mm in distal right coronary artery (RCA), left circumflex (LCx) artery was also aneurysmal 3.3 mm (*z* +4.78) (moderate size). Left ventricular function was maintained.

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How to cite this article: Sarkar SD, Pal P, Giri PP, *et al.* Multiple Giant Coronary Aneurysms in an Infant with Prolonged Fever. Pediatr Inf Dis 2021;3(1):43–45.

Source of support: Nil

Conflict of interest: None

The baby was promptly started on IVIG 2 g/kg along with aspirin 50 mg/kg and low molecular weight heparin (LMWH). Since fever

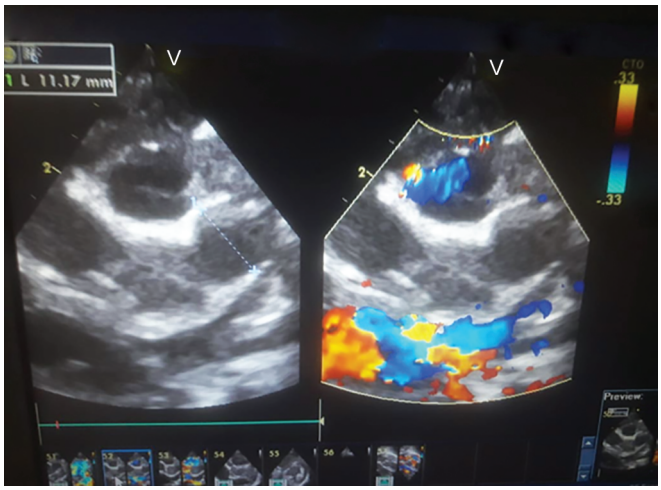

Fig. 1: Giant aneurysms in left main coronary artery and left anterior descending coronary artery with marked increase in perivasacular echogenicity

persisted, and also to intensify therapy in the presence of multiple aneurysms, infliximab 5 mg/kg was administered after 48 hours of completion of IVIG infusion. The child became afebrile within 24 hours of infliximab with normalization of CRP.

Repeat echocardiography after 5 days showed a further increase in the aneurysms with an increased clot size of 7.8 mm × 2.1 mm. In the absence of readily available tissue plasminogen activator, thrombolysis was initiated with Streptokinase at a loading dose of 2000 IU/kg over 30 minutes, followed by a maintenance dose of 500 IU/kg per hour. LMWH and aspirin at 5 mg/kg were continued. Echocardiography on the following day showed a decrease in the clot size. Streptokinase was increased to 700 IU/kg and repeat echocardiography after 24 hours showed complete dissolution of the clot. Streptokinase was stopped after 48 hours of continuous infusion and the baby was finally discharged on LMWH, clopidogrel, and aspirin.

Echocardiography repeated after 2 weeks showed that the size of the aneurysms was unchanged but there was no clot. LMWH was converted to oral warfarin with a target INR of 2–3. At 18 months follow-up, the child continues to have persistent giant aneurysms with minimal regression in size of the aneurysms.

Discussion

KD is diagnosed clinically based on persistent fever ≥5 days in combination with polymorphous rash, cervical lymphadenopathy, bilateral nonpurulent conjunctivitis, changes in the mucous membrane of the tongue and lips (strawberry tongue, dry red cracked lips), and extremity changes (swelling and/or redness of the palms and soles, finger toes desquamation in the subacute phase). "Complete" KD is defined by fever and ≥4 of the five symptoms. It is important to appreciate that all the clinical findings may not be present at a time in a patient: they may appear successively instead of simultaneously. However, in the recent American Heart Association (AHA) guidelines, the diagnosis can be made earlier with only 4 days of fever if four or more of the symptoms are unambiguously present. The AHA has also created an algorithm for diagnosis of "incomplete" KD in case ≤3 criteria are present, which includes CAAs on echocardiography and/or laboratory abnormalities.[4] The diagnosis may be even more difficult in early infancy when incomplete and atypical presentation is commonly seen, thereby resulting in delayed diagnosis.[5] In our case, the baby presented with only persistent fever without any of the other supportive clinical finding. In the absence of negative cultures, the high CRP, neutrophilic leukocytosis, normocytic anemia, progressive thrombocytosis, and the young age of presentation lead to the suspicion of KD, which was confirmed by the presence of significant coronary aneurysms.

Coronary artery dilatation *z*-score ≥2.5 is considered significant and aneurysms with *z*-score ≥10 are considered giant aneurysms. In our patient, the proximal part of LMCA had an aneurysm with *z*-score +16.1 and there was a clot in LAD. These warranted the initiation of anticoagulant therapy with LMWH.

Treatment with 2 g/kg of IVIG, within the first 5–10 days of the illness effectively decreases coronary artery aneurysm formation. IVIG should also be given to patients presenting after the 10th day of illness if they have either ongoing inflammation manifested by persistent fever (after excluding other causes) or elevated CRP/ESR and/or aneurysm formation. Our patient was diagnosed after 15 days of illness and had raised CRP and giant coronary aneurysms, and hence IVIG was initiated immediately.

The majority of patients respond rapidly to IVIG, but about one-fifth of all patients do not respond or have recurrent fever within 36–48 hours after IVIG administration. These patients have an increased risk of developing CAA.

In Japan, scientists have developed risk–score systems to identify patients with an increased risk of developing IVIG resistance.[6] Unfortunately, there is not enough data to conclusively state how far these scoring systems are effective in predicting IVIG resistance in the Indian population. A possible way of decreasing IVIG resistance is intensification of the initial treatment. Dionne et al.[7] have shown that intensifying the treatment with either IFX or corticosteroids independently protect against the progression of coronary artery dilatation in patients with CAA at diagnosis. Since the baby was IVIG resistant and had aneurysms at diagnosis, infliximab was administered.

Giant CAAs may have grave long-term sequelae. There may be thrombosis within the CAA and perfusion abnormalities distal to the CAA, or there may be stenosis just proximal or distal to the CAA. In a study by Friedman et al., in 90 patients with giant CAA at diagnosis (*z*-score ≥10), 21 suffered from major adverse cardiac events (MACE).[8] This shows that patients with giant CAA are at considerable risk for MACE and the risk persists even years after the acute phase.

Anticoagulation in KD is recommended for the following: (1) giant aneurysm, multiple or complex aneurysms, and presence of thrombus; (2) associated stenosis; (3) peripheral gangrene. Initiate with subcutaneous LMWH followed by oral warfarin to maintain INR of 2–2.5. Since maintaining the recommended INR is very difficult in infancy and young children, one may continue with the LMWH for a more stable response.

For arterial thrombosis, peripheral gangrene-thrombolytics have been tried in addition to anticoagulation.[4] Thrombolytic treatment helps in lysing a developing thrombus within a giant CAA and also in preventing distal ischemia due to such thrombus.[9] Urokinase, streptokinase, and tissue-type plasminogen have all been used for the lysis of coronary artery thrombosis. Following thrombolysis, peripheral arterial blood flow is restored, and then perfusion is maintained by heparin followed by oral anticoagulation in the long-term. If these treatments fail, a variety of invasive approaches are tried, including percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. In our patient, there was a giant aneurysm (*z*-score 16.1) and the presence of clot in LAD. Since the clot was increasing in size in spite of LMWH on follow-up echocardiography, fearing an impending MACE, prompt decision was taken to initiate thrombolysis. Post thrombolysis LMWH was continued together with aspirin and clopidogrel, and subsequently on follow-up, LMWH was converted to warfarin.

Usually within the first five years, some CAAs may regress but the degree of return to normalcy seems to be highly dependent on the degree of dilatation.[8,10] While the lumen diameter may regress, the vascular wall elasticity may stay damaged and studies have shown persistent impaired inadequate dilatation in the face of increased cardiac demand.[11] In our patient, though there was resolution of the clot, the baby continues to have persistent giant aneurysms.

Conclusion

Kawasaki disease can have myriad presentations. The patient may not demonstrate all the classic clinical features or the features may be temporally dissociated, confusing the diagnosis. This specially

holds true for patients presenting in early infancy, when they may present with just fever or excess irritability. Timely diagnosis and intervention can save the child from severe cardiovascular accidents and death. Interventions such as thrombolysis and anticoagulation are instrumental in decreasing the mortality and morbidity in special circumstances.

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GLOBAL CARDIOLOGY SCIENCE & PRACTICE

Review article

The emergence of Kawasaki disease in India and China

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ABSTRACT

Kawasaki disease (KD) is recognized as a leading cause of acquired heart disease in children in developed countries. Although global in distribution, Japan records the highest incidence of KD in the world. Epidemiological reports from the two most populous countries in the world, namely China and India, indicate that KD is now being increasingly recognized. Whether this increased reporting is due to increased ascertainment, or is due to a true increase in incidence, remains a matter of conjecture. The diagnosis and management of KD in developing countries is a challenging proposition. In this review we highlight some of the difficulties faced by physicians in managing children with KD in resource-constrained settings.

http://dx.doi.org/10.21542/gcsp.2017.21

Received: 16 June 2017
Accepted: 19 September 2017

Cite this article as: Jiao F, Jindal AK, Pandiarajan V, Khubchandani R, Kamath N, Sabui T, Mondal R, Pal P, Singh S. The emergence of Kawasaki disease in India and China, Global Cardiology Science and Practice 2017:21 http://dx.doi.org/10.21542/gcsp.2017.21

INTRODUCTION

Kawasaki disease (KD) is recognized as a leading cause of acquired heart disease in children in developed countries, having replaced acute rheumatic fever as the most common cause. Over 60 countries across the world have reported KD to date, with robust epidemiological data available only from Japan, Taiwan, Korea, USA, UK, and Australia[1,2]. However, it should be noted that varying methodologies have been used to study the epidemiology of KD in different countries. These include passive surveillance from past hospital records, case registries, and active surveillance. Over the last two decades, awareness of KD amongst pediatricians in the world's two most populous countries - China and India - has increased significantly and this condition is being reported increasingly frequently. There is anecdotal evidence that KD may soon replace rheumatic fever to become the commonest cause of acquired heart disease in children in both these countries.

EPIDEMIOLOGY OF KD

Japan records the highest number of cases of KD in the world, with ~12,000 new cases being identified each year[3]. An updated estimation of the national incidence rate for KD is 322 per 100,000 children <5 years[4]. Approximately 85% of affected children with KD are younger than 5 years, although Indian data suggest that almost a third of patients are older. The male to female ratio is approximately 1.5:1[1]. In India there has been a steady increase in the number of cases diagnosed to have KD since the mid-1990s[5]. At many centres in India, KD has surpassed Henoch Schonlein purpura as the most common childhood vasculitic disorder[6].

Unique epidemiological patterns have been identified in different regions. For instance, incidence rates in Far East Asian countries like Japan, Korea, and Taiwan are well above 50/100,000 children <5 years and, for reasons that are not clear, the incidence rates have continued to rise over the last 2 decades[2]. However, incidence in the United States, Canada, Australia and the European Union is around 4-25/100,000 children <5 years and these rates have reached a plateau[2].

Data from the two most populous countries in the world, namely China and India, indicate that KD is now being increasingly recognized[2]. Whether this increased reporting is due to increased recognition of KD, or is a true increase in incidence, remains a matter of conjecture. Robust nationwide data are not available from either of these countries.

Epidemiology in China

Regional epidemiological studies are available from China that show varying incidence in different geographic regions[7,8]. However, the overall trend in incidence of KD appears to be on the rise[2]. A questionnaire-based study data from Beijing (2000–04)showed an increase in incidence from 40.9 to 55.1 per 100,000 children <5 years[7]. Similar trends were noted in Shanghai where the incidence increased from 27.3 per 100,000 (1998–2002) to 46.3 per 100,000 in 2007[9]. Mean incidence in Sichuan Province was documented to be 7.1 per 100,000 children <5 years[10]. Data from Hong Kong also showed an increase in incidence from 26 per 100,000 children <5 years in 1994 to 39 per 100,000 in 2000 and to 74 per 100,000 in 2011[2].

Epidemiology in India

Before 1990, there were only 3 published reports of KD from India and the first report was published by Taneja et al. in 1977. However, over the last 20 years, several centres in India have started reporting KD[11–13]. A PubMed search with the terms "KD AND India" shows

161 citations with only 8 before 2000. The first two published case series came from Thiruvananthapuram in South India and Chandigarh in North India in the year 1997[14,15]. Since then, KD has been recognized in almost all parts of the country. A telephonic and questionnaire-based survey among physicians in India showed that KD is definitely being increasingly recognized in India. This could be either due to an actual rise in number of cases or due to increased awareness amongst pediatricians[16].

Many senior pediatricians in India are of the opinion that KD was virtually non-existent in the country before the 1980s. India has witnessed a considerable surge in industrialization and economic productivity since the early 1990s. This coincided with the rise in number of cases of KD being reported from various parts of the country. Moreover, Kerala, which is one of the most developed states in India, also reports the largest number of cases of KD. Many physicians and pediatricians are of the view that rise in KD coincided with the fall of incidence of diarrhea and better vaccination coverage rates[16].

A hospital based study from Chandigarh, North India showed an increase in incidence of KD from 0.51 per 100,000 children <15 years of age in the year 1994 to 4.5 per 100,000 children <15 years of age in the year 2007[5]. Peak incidence was noted in of October with a nadir in February. These incidence rates were speculated to be underestimates because of unrecognized and missed cases in the community due to lack of awareness amongst physicians and pediatricians. A follow-up study on the same pattern found that the mean incidence of KD at Chandigarh during the period 2009–2014 was 5.35/100,000 children <5 years[17].

ISSUES IN DIAGNOSIS OF KD IN DEVELOPING COUNTRIES

1. For many physicians in developing countries like China and India, where the burden of infectious disease is high, KD is still not commonly included in the differential diagnosis of children presenting with fever. Antimicrobials are commonly prescribed for febrile episodes, and if the fever does not subside, a broader spectrum antimicrobial is often substituted. Some of the cardinal manifestations of KD (e.g., fever, rash and lymphadenitis) are also seen in many paediatric infectious diseases and it is not surprising that KD gets overlooked in such a milieu. Paediatricians in developing countries need to be sensitized about KD.
2. The presence of associated viral infections may not rule out the possibility of KD as both may co-exist in the same patient.
3. Although KD is now being diagnosed in most parts of China and India, there is no shortage of sceptics who refute the diagnosis of KD[18]. If diagnosis of KD is proffered by a paediatrician and the parents seek a second opinion, it is not unusual to encounter situations where this possibility is negated completely. As a result the patients may not get appropriate treatment for KD even when the condition has been correctly diagnosed.
4. In areas where awareness about KD is still not optimal, the treating paediatricians may not be aware that the clinical features of KD are transient and may change from day to day. As the fever persists, parents often seek multiple consultations. As a result many of the clinical findings that were present during the first few days of the disease may have subsided by the time the child is seen by another paediatrician - this often results in missed diagnosis.
5. Although KD is now being commonly recognized by paediatricians, it is not a part of undergraduate teaching curriculum in most medical schools. It is also not given

the importance that it deserves in post-graduate medical curricula. Many adult physicians and cardiologists are still unaware of the devastating coronary sequelae associated with this condition.

ISSUES RELATED TO ECHOCARDIOGRAPHY IN KD

1. It is important to understand that echocardiography performed during the first 7 days of fever can never rule out a diagnosis of KD. If abnormalities are detected, it may confirm a clinical suspicion of KD. In developing countries like China and India, the echocardiography for KD is usually carried out by an adult cardiologist or a technologist (especially in China), who may not have enough expertise to perform echocardiographic evaluation of the coronary arteries in young infants. This is due to a paucity of trained paediatric cardiologists in developing countries.
2. Further, it is not unusual for the cardiologist to refute a diagnosis of KD on the basis of normal echocardiographic findings. In such situations when there is a difference of opinion between the paediatrician and the cardiologist, it becomes very difficult for the parents to decide on a reasonable course of action. Many parents may, in fact, opt not to go for treatment even when they have been told that there is no doubt about the diagnosis of KD. The cost of treatment may also be a factor in this decision.
3. The interpretation of echocardiographic findings is another issue that has not been adequately addressed in developing countries such as China and India. Many centres are still using the Japanese criteria for defining coronary artery abnormalities. Although these criteria are useful for initial screening, for more accurate assessments it is mandatory to use Z scores (internal dimension of the coronary artery expressed as the standard deviation from the mean normalized for body surface area)[19]. Though some centres in India (including Chandigarh, Kolkata and Mumbai) have starting using Z scores for assessment of coronary artery diameters, this is still not a routine practice in many parts of the country. The situation in China is similar. As a result there could be problems in interpreting the echocardiographic findings in a given child. Findings on echocardiographic examinations carried out at different centres are often not comparable and this adds to the diagnostic dilemma.

ROLE OF NON-INVASIVE CORONARY ANGIOGRAPHY IN KD

Newer imaging modalities, such as dual source 128-slice computed tomography (DSCT) coronary angiography and magnetic resonance coronary angiography, are not being used frequently in developing countries as facilities are limited. At Chandigarh we have been using DSCT coronary angiography since 2014. This technique has been found to be extremely useful in the follow-up of patients with KD. Abnormalities in distal segments of coronary arteries that were missed on echocardiography could be picked up by this technique. Similarly, abnormalities in the circumflex coronary artery that may be difficult to identify on echocardiography are picked up by this imaging technique. However, the expertise to carry out and interpret the findings of CT coronary angiography is a significant barrier for using this imaging modality more widely in developing countries[20–22].

THE DILEMMA OF 'INCOMPLETE' AND 'ATYPICAL' KD

1. Though the terms 'incomplete' and 'atypical' KD have, at times, been used interchangeably, they represent clinically distinct conditions. A child is considered to have incomplete KD when there are fewer than 4 clinical features in the presence

of fever[1]. "Atypical KD" should be used in the presence of an unusual or odd manifestation of KD (e.g., nephritis or central nervous system complication)[23–26]. Incomplete KD is especially difficult to recognize as the diagnosis can be very difficult even for an experienced physician[27]. Young infants often have incomplete forms of KD and, in developing countries where infectious diseases are very common, may often be misdiagnosed to have viral exanthemata[28]. Incomplete KD is, by no means, a mild form of KD. On the contrary, such children may have significant coronary artery sequelae as the diagnosis and treatment are often delayed[29].

2. All paediatricians need to be familiar with some of the pathognomonic clinical findings of KD that are not emphasized in the American Heart Association (AHA) diagnostic criteria[30]. These include reactivation of the Bacillus Calmette–Guérin (BCG) injection site[29], sterile pyuria[31], perineal peeling, arthritis, myocarditis, and hydrops of gall bladder. In difficult cases it is these clinical findings that may help the paediatrician in arriving at a diagnosis. Pro-BNP (Brain natriuretic peptide) estimation has recently been evaluated for inclusion in the diagnostic criteria of KD[33,34]. However, this laboratory investigation needs further validation for use in clinical practice.

CONSEQUENCES OF A MISSED DIAGNOSIS OF KD

No paediatrician can afford to miss a diagnosis of KD as the consequences can be grave[35,36]. The diagnosis of KD has to be considered upfront in all children where the fever persists for 5 days or more, even in the context of a developing country. The risk of coronary artery involvement is nearly 1 in 4 cases (25%) if left untreated[37]. Once giant coronary aneurysms develop, they are almost always irreversible.[1,37] This risk can be significantly curtailed to less than 3% if intravenous immunoglobulin is administered within the first 10–12 days of fever. Missed KD in childhood can result in long-term coronary sequelae and affected patients can present in young adulthood with coronary ischemia, myocarditis, myocardial infarction, arrhythmias or sudden death. Thus the early diagnosis and prompt management of KD in childhood can have important implications for long-term cardiac morbidity. Adult cardiologists need to be familiar with these sequelae. At present, most adult cardiologists, especially in developing countries, may not be conversant with the ravages of missed KD in childhood. A recent publication from India demonstrates that this is slowly changing[38].

ISSUES IN THE MANAGEMENT OF KD

1. The treatment of KD involves use of intravenous immunoglobulin (IVIG)[1]. It is an expensive product and many families in developing countries may not be in a position to afford this treatment. IVIG is available free of cost in some regions (e.g., Shanghai in China; New Delhi, West Bengal and Kerala in India).
2. Although availability of IVIG is a major challenge in some developing countries, this is not a problem in either China or India. With the increased ascertainment of cases of KD in these countries, one can expect a major challenge to the existing health-care systems.

OTHER FORMS OF THERAPY FOR KD

In situations where administration of IVIG is not feasible for reasons of availability or affordability, one can consider alternative modes of therapy like glucocorticoids as a

desperate measure. However, it should be understood that head to head trials comparing IVIG and glucocorticoids have never been carried out and, considering the proven efficacy of IVIG in KD, it may not be ethically possible to conduct such trials in the future. Such trials may only be feasible in countries where access to IVIG is extremely difficult.

OUTCOMES OF KD

The mortality reported in our cohort of children with KD from Chandigarh is 0.8%[39]. This is significantly higher than mortality figures of ≤0.04% reported from developed countries[35,39]. This increased mortality is largely attributed to delays in diagnosis and institution of therapy, especially in infants. In addition, the burden of coronary artery disease that may emerge if KD patients remain under-diagnosed and untreated will be a significant contributory factor to the long-term cardiac morbidity and mortality in these patients. Thus, KD is by no means a one-time disease of childhood. It has significant public health importance, especially for developing countries like China and India where the diagnosis of KD is often missed or delayed.

Epidemiologic data suggest that by 2030, in USA the estimated prevalence of KD would be 1 in 1,600 individuals[40]; in Taiwan the figure would be 1 in 700 individuals[41]. It is difficult to develop similar projections for developing countries because of lack of accurate epidemiologic data on KD in these countries. However, it is very likely that the consequences of missed KD in childhood in these countries will impact the public health resources in the years to come.

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