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ORIGINAL ARTICLE

Profile of Children with Kawasaki Disease Associated with Tropical Infections

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Abstract

Objective To describe various infectious triggers for Kawasaki disease (KD) in India.

Methods A series of 10 children with diagnosed infections who developed KD during their course of illness has been presented. They were diagnosed by the American Heart Association (AHA) 2017 guidelines. Echocardiography was done to check for coronary artery dilation. Treatment was instituted as per standard protocol.

Results Kawasaki disease was diagnosed in 8 boys and 2 girls, aged 1 mo to 11 y. These children were being treated for dengue, chikungunya, SARS-CoV-2, hepatitis A, tuberculosis, brucellosis, disseminated staphylococcal sepsis, scrub typhus, and enteric fever.

Conclusions Kawasaki disease has been associated with infectious triggers. It should be considered in febrile patients with mucocutaneous involvement or in nonresponsive sepsis, despite adequate therapy.

Keywords Coronary artery aneurysm · Infection · Kawasaki disease

Introduction

Kawasaki disease (KD), originally called 'mucocutaneous lymph node syndrome' is the most common vasculitis of childhood. The diagnosis is mainly clinical based on American Heart Association (AHA) 2017 criteria [1]. There are no pathognomic laboratory tests that can be used to confirm the diagnosis. It is often missed because the clinical features of KD overlap with common childhood infections like measles, dengue, scarlet fever, parvovirus B19, and other viral exanthems. The etiology is still unknown, though multiple theories have been proposed based on available epidemiological data [2]. The current consensus is that an infectious trigger initiates an abnormal and robust innate inflammatory response in genetically predisposed children [3].

The most frequent association of KD is with viral infections like Epstein–Barr virus, cytomegalovirus, adenovirus, parvovirus B19, herpes virus 6, parainfluenza type 3, measles, rotavirus, dengue virus, human immunodeficiency virus, varicella, H1N1 2009 pandemic influenza, coronaviruses, and coxsackie B3 virus [4–19]. Even bacteria like *Staphylococcus aureus* and Streptococcus pyogenes have been implicated [20]. Most of these studies are from *U.S.A., China, Korea, Taiwan, and Australia* [21]. There is lack of literature from India regarding the profile of KD associated with infections. A series of 10 cases with an infection associated KD is reported in this paper.

Material and Methods

This was a single-center prospective case review of children who were initially admitted with acute febrile illness of infectious etiology. These children were diagnosed to have an infection based on clinical and laboratory findings. They did not show improvement or deteriorated despite adequate antibiotic and supportive therapy. On further investigation, they were diagnosed as KD according to AHA 2017 criteria [1]. Patients with fever, who fulfill 4 of the 5 principal clinical features are said to have classical/complete Kawasaki disease. Those who meet less than 4 criteria are classified as incomplete Kawasaki disease. All such patients admitted

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between January 2019 and January 2021 were included. The demographic profile, anthropometry, clinical features, laboratory findings (complete blood count, liver function tests, kidney function tests, ESR, CRP, ferritin, fibrinogen, D-dimer), echocardiographic findings, and treatment details were collected from case records and entered in a prestructured proforma. Informed consent from patient caregiver and permission from Institution ethics committee was obtained.

Data entry was done in Microsoft excel sheet and analyzed. Measures of central tendency to find mean and median were used. R software was used for statistical analysis.

Table 1 Demographic and clinical profile of the children with infection-associated KD

Patient characteristics (number)	*N* = 10
Age (months, median; IQR)	57; 24–108
Gender (male:female)	8:2
Duration of fever [days, (median; IQR)]	5; 5–6
Rash (number of patients, %)	4; 40
Mucositis (number of patients, %)	8; 80
Lymphadenopathy (number of patients, %)	3; 30
Eye redness (number of patients, %)	9; 90
Desquamation of the skin (number of patients, %)	8; 80
Extremity edema (number of patients, %)	8; 80
Infectious etiology	*N* = 10
Staphylococcus aureus	2
Rickettsial (scrub typhus)	1
Brucella + tuberculosis	1
Dengue + chikungunya + staphylococcus (coinfection)	1
Hepatitis A	1
COVID-19 (RT-PCR+)	1
Pseudomonas	1
Typhoid	1
Dengue	1

COVID-19 Coronavirus disease 2019; *IQR* Interquartile range; *KD* Kawasaki disease; *RT-PCR* Reverse-transcription polymerase chain reaction

Result

Ten patients were enrolled in the study. The baseline demographic, clinical details, and associated infections are shown in Table 1 and 2. Six cases (60%) with infections responded to antimicrobials and their fever resolved. They subsequently had fever with principal clinical findings and echocardiography, that was suggestive of KD. Four patients (40%) had persistent fever despite appropriate antimicrobial initiation, with new onset principal clinical findings of KD. This was confirmed by echocardiography. The median duration of recurrence of fever or new onset principal clinical findings with fever was 5 d. The median age of the patients was 57 mo (IQR 24, 108). The disease was 4 times more common in boys. The presenting complaints included fever, rash, extremity edema, and mucositis with cracking and fissuring of lips.

Complete and incomplete KD were seen in 5 children each. There were no atypical cases showing central nervous system, renal, or musculoskeletal system involvement [22]. The spectrum included both viral and bacterial infections as shown in Table 2. One of the cases was diagnosed to have bacterial and viral coinfection based on blood culture showing methicillin-resistant *Staphylococcus aureus* (MRSA) along with NS1 antigen (nonstructural protein 1) positive for dengue. He was also found to have IgM positive

Table 2 Clinical profile of patients

Etiology	Fever	Oral mucositis	Conjunctivitis	Rash	Edema/Desquamation	Lymphad-enopathy	ESR/CRP ↑	Echocardiogram
Staphylococcus	+	−	+	+	+	+	+	+
COVID-19	+	+	+	+	+	−	+	+
Staphylococcus + dengue + chikungunya	+	+	+	−	+	−	+	+
Dengue	+	+	−	+	+	−	+	+
Brucella	+	+	+	−	+	+	+	+
Scrub typhus	+	+	+	+	+	−	+	+
Staphylococcus	+	+	+	−	−	−	+	−
Hepatitis A	+	−	+	−	+	−	+	+
Pseudomonas	+	+	+	−	−	−	+	+
Enteric fever	+	+	+	−	+	+	+	−

COVID-19 Coronavirus disease 2019; *CRP* C-reactive protein; *ESR* Erythrocyte sedimentation rate

+ indicates presence and − indicates absence of a clinical feature

for chikungunya. The laboratory investigations have been depicted in Table 3. The CRP and ESR values were raised over AHA defined cutoff of over 3 mg/dL and 30 mm/h, respectively in all the patients. The echocardiography findings at diagnosis and follow-up of the patients have been described in Table 4. Eight children (80%) with KD had abnormal echocardiography findings at diagnosis. Four children had coronary artery aneurysms (CAA) at diagnosis as indicated by z scores of ≥ 2.5. Two children had coronary dilatation with coronary *z* scores of 2–2.5. Two others had normal coronary *z* scores at diagnosis but showed a decrease of ≥ 1 SD score at follow-up and were classified as coronary dilatation as per AHA 2017 guidelines [1]. One of the patients showed periarterial enhancement and lack of tapering at the time of diagnosis. Another child had normal echocardiography and 4 principal clinical findings of KD. Out of these 8 children, 2 had persistent CAA on follow-up and remaining showed normalization of echocardiographic findings on follow-up.

All patients received IVIG and aspirin at diagnosis. Eight (80%) children responded to first dose of IVIG and aspirin. Two patients required additional therapy like second dose of IVIG, steroids, and infliximab. Case 5 needed infliximab infusion. Both IVIG-resistant patients had CAA

Table 3 Laboratory indices of children with infection-associated KD

Parameter	Median (IQR)
Hemoglobin (g/dL) (median, IQR)	9.1 (7.9–10.2)
Total lymphocyte count (thousand/mm^3) (median, IQR)	13.25 (10.10–23.40)
Absolute neutrophil count (thousand/mm^3) (median, IQR)	7.31 (6.7–18.2)
Platelets (lacs/mm^3) (median, IQR)	3.11 (1.9–4.8)
ESR (mm/first hour) (median, IQR)	31.5 (28–37)[a]
CRP (mg/dL) (median, IQR)	73 (43–109)[a]
D-dimer (ng/mL) (median, IQR)	693 (323–990)
Fibrinogen (mg/dL) (median, IQR)	217.5 (181.2–299.5)
Ferritin (ng/mL) (median, IQR)	415.5 (267.5–745.2)
AST (IU/L) (median, IQR)	43.5 (29–97)
ALT (IU/L) (median, IQR)	54 (25–178)
Albumin (g/dL) (median, IQR)	2.9 (2.3–3.1)
Triglycerides (mg/dL) (median, IQR)	165 (133–214)
Urea (mg/dL) (median, IQR)	26 (19–48)
Creatinine (mg/dL) (median, IQR)	0.35 (0.2–0.5)

CRP C-reactive protein; *ESR* Erythrocyte sedimentation rate; *IQR* Interquartile range; *KD* Kawasaki disease

[a]indicates raised median values

Table 4 Echocardiography coronary artery *z* scores at admission and follow-up

Case no	Coronary artery *z* score at admission			Coronary artery *z* score at 1 mo follow-up		
	LAD	RCA	LMCA	LAD	RCA	LMCA
1	−0.06	−0.11	+1.35	−0.96	−1.38[b]	−0.07[b]
2	+1.32	+2.0	+1.02	+0.04[b]	+0.3[b]	+0.16
3	+1.13	+3.67[a]	+2.36	−0.72	+1.75	−1.12
4	+1.84	+1.04	+2.34	−0.79[b]	+0.03[b]	−1.09[b]
5	+3.06[a]	+3.07[a]	+3.84[a]	+2.7	+1.9	+3.1
6	+3.2[a]	+1.53	+1.54	−0.07	+1.28	−1.17
7	+1.56	+0.40	+1.42	+1.5	+0.4	+1.4
8	+1.34	+0.32	+1.8	+0.42	+0.10	−0.19[b]
9	+2.7	+3.5[a]	+1.5	+3.07	+2.08	+1.28
10	+0.14	+0.52	+0.18	+0.29	+0.61	+0.06

LAD Left anterior descending artery; *LMCA* Left main circumflex artery; *RCA* Right coronary artery

[a]Coronary artery aneurysm (*z* score > 2)

[b]dilated coronary artery; > 1 *z* score decrease following treatment

that regressed following second-line therapy. In the present series, no child had myocarditis, Kawasaki disease shock syndrome (KDSS), or macrophage activation syndrome (MAS). None of the patients required vasopressors, ventilator support, or anticoagulants.

Discussion

The paradigm of KD has changed in the setting of SARS-CoV-2 pandemic in recent times [23, 24]. It has come back in focus with emergence of multiple reports of pediatric multisystem inflammatory disease (PMIS) or multisystem inflammatory syndrome in children (MIS-C) with KD-like features often complicated with myocarditis, shock, and MAS [25]. The AHA 2017 guidelines have simplified the approach, diagnosis, and treatment of KD in children. It has also emphasized the occurrence of KD associated with preexisting infections. It is mainly described in context of multiple known viral infections [26]. In the present series, various infectious triggers for KD in India are described. These included different bacteria like MRSA, brucella, salmonella, pseudomonas, and rickettsia and viruses such as the SARS-CoV-2, dengue, chikungunya virus, and hepatitis A. It is well known that these infections are endemic to the Indian subcontinent, but there is scarcity of literature from India that shows association of KD in presence of these tropical infections.

In the patients included in the study, the clinical features included 5–6 d of fever with conjunctival injection, rash, and mucositis with cracking and fissuring of lips. Children with febrile illnesses are often treated with antibiotics. There is a common clinical practice to upgrade antibiotics if fever does not subside. The possibility of KD in such patients must be considered, especially in presence of subtle signs like skin rash or extremity edema, cracking of lips, strawberry tongue, conjunctivitis, and lymphadenopathy. These signs are often attributed to drug allergies/reactions, poor hygiene, micronutrient deficiencies or the underlying infection. The alternative line of treatment (IVIG, aspirin or steroids) can then be considered, thereby preventing antibiotic misuse and coexisting emergence of resistance [27].

The values of ESR and CRP were raised above the AHA-defined cutoff for diagnosis of KD in all children included in the study. Literature review shows that the ESR is elevated during acute phase but is an unreliable marker following IVIG administration. CRP is another nonspecific marker that correlates with the risk of CAA. Inflammatory biomarkers such as procalcitonin, total leucocyte count, mean platelet volume, platelet distribution width, peripheral blood eosinophilia are nonspecific and of limited clinical use [28]. N-terminal pro b-type natriuretic peptide (NT-pro-BNP) is a cardioselective biomarker useful for diagnosis of KD, although its values vary with age. Prospective pediatric studies evaluating the role of NT-pro-BNP in the diagnosis of KD recommend cutoff values of between 190 ng/L and 260 ng/L [29]. In children where there is high suspicion of KD, this may be used as an adjunct to the clinical and echocardiography findings.

In the present study, 4 (40%) children had CAA and 4 (40%) had dilated coronary arteries as per AHA-2017 criteria. This is higher than the overall incidence of CAA in KD, i.e., 15–20% [1]. A possible reason for this could be that pre-existing infections can also contribute to coronary dilation [30, 31] or time spent awaiting antimicrobial response in a febrile patient or multiple consultations sought by parents before diagnosis is made. Reyna et al. showed coronary artery dilatation in 26% of non-Kawasaki febrile viral exanthematous illnesses. They have explained this phenomenon by compensatory increase in coronary artery blood flow to meet the myocardial oxygen demand in fever and tachycardia [30]. In a study done by Chbeir et al., cardiac abnormalities were noted in an initial echocardiogram in 31% of patients and in 11% of the echocardiograms performed at 6 wk after disease onset. They have explained this higher involvement by including any abnormal echocardiographic findings, in particular perivascular brightness of the coronary arteries [32]. The authors hypothesize that infections in a genetically predisposed child lead to hyper-responsiveness of the innate immune pathway. The accompanying inflammation and cytokine stormcontributes to increased incidence ofcoronary artery involvement.

Management of KD consists of IVIG infusion at a dose of 2 g/kg given over 12 h and 80–100 mg/kg aspirin. In children with myocarditis the infusion may be given over 18–24 h to avoid fluid overload. In case of varicella- or influenza-triggered KD, high-dose aspirin should not be given. It can be followed with an alternative antiplatelet agent (clopidogrel), once afebrile or low-dose aspirin as it does not pose the risk of Reyes syndrome [1]. Persistence of fever beyond 36 h after completion of IVIG indicates IVIG resistance and warrants treatment with second line therapies. There might be clinical confusion regarding the need for second-line therapy for KD due to coexisting infection. The authors suggest that echocardiography along with NT-pro-BNP levels may help guide therapy in that case. In presence of CAA/coronary artery dilatation it may be prudent to give a second dose of IVIG with or without steroids. Only 2 patients in the present study needed second-line therapy including infliximab. Though further research is needed to make a universal recommendation. The patient with dengue, in the present study, had an improving platelet count when KD was considered and aspirin was initiated once platelets were over 1,00,000/mm^3.

This study is the first of its kind to show the spectrum of infections that can lead to KD in a tropical country like

India. In the present series no child had myocarditis, KDSS, or MAS. Early identification of KD in these cases and prompt appropriate therapy may prevent long-term cardiac complications [33]. However, the limitation of the study is that the sample size is small and it has been conducted over a short time period.

Conclusion

In the present series of 10 children who developed KD in the course of their infectious illness, the clinical presentation included fever with conjunctival injection, rash and mucositis with cracking and fissuring of lips emerging as the most common signs. Most of the patients showed echocardiographic abnormalities but responded favorably to IVIG. This highlights that the presence of a pre-existing infection does not rule out the possibility of KD. The signs are often subtle and may be missed or attributed to drug allergies/reaction, poor hygiene, and micronutrient deficiencies or the underlying infection. Antibiotics are upgraded in these scenarios leading to unnecessary antibiotic usage and emergence of resistance. Increased awareness would help in early diagnosis, prompt treatment, and preventions of long-term cardiac complications. Easily available biomarkers like NT-pro-BNP may help in cases where clinical and echocardiography findings are inconclusive.

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Authors' Contributions AM, DM, VK, and AM conceptualized the idea, drafted the manuscript, and managed the patients; SY helped in collection and analysis of the data; AR, KD, HM, and SS helped in management of the patients. VK will act as the guarantor for this paper.

Declarations

Conflict of Interest None.

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