Clinical profile of Kawasaki disease in children admitted at a tertiary care hospital of North India and their short-term follow-up

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ABSTRACT

Aim : **The aim of this study was to evaluate presenting symptoms, clinical features, and laboratory tests for the diagnosis of Kawasaki disease (KD) in children and their short-term follow-up at a tertiary care hospital of North India from April 2017 to March 2020.**

Materials and Methods : **A total of 31 children (23 boys and 8 girls) up to 10 years of age were included in this study. The diagnosis of KD was made as per the American Heart Association 2017 guidelines. Clinical features, laboratory parameters, and coronary involvement were compared between the complete and incomplete KD groups.**

Results : **The incidence of complete versus incomplete KD was 19 (61.2%) versus 12 (38.7%) children, respectively. Change in extremities and oral mucosal changes were more encountered in the complete KD group as compared to the incomplete KD group (100% vs. 58.3%, $P = 0.004$, and 78.9% vs. 33.3%, $P = 0.002$, respectively). Coronary artery aneurysm was seen in 54% of the patients on echocardiography which was greater in the incomplete KD group (83.3%) as compared to the complete KD group (36.8%). The median time from the onset of symptoms to intravenous immunoglobulin infusion was <10 days in 84.2% of the patients with complete KD versus 41.7% with incomplete KD which was statistically significant. Fifty percent of the children with coronary ectasia and small aneurysm had normal coronaries at follow-up of 6 months.**

Conclusion : **KD is probably underdiagnosed in most developing countries, like that of ours, and requires a high index of suspicion.**

Keywords : Complete and incomplete Kawasaki disease, coronary artery aneurysms, Kawasaki disease, transient coronary dilatation

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of early childhood considered the leading cause of acquired heart disease in children in developed countries. Cardiac lesions are a hallmark of KD, and coronary artery aneurysms (CAAs) develop in 20% of untreated children and can lead to coronary stenosis, myocardial infarction, or sudden death. Pericarditis complicated by cardiac tamponade or myocarditis associated with myocardial dysfunction can also occur during the acute phase.[1,2]

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Despite almost 50 years of research, the etiology of KD remains unknown. An infectious trigger which causes an excessive inflammatory response in genetically predisposed children is a widespread hypothesis, but no specific pathogen has been identified yet.[3]

In developed countries, KD is the most common cause of acquired heart disease in children. Even in developing countries, KD is now being increasingly reported, and it is emerging as one of the leading causes of acquired heart disease in children.[4-6] However, no age group seems to be exempt from developing KD, and this disease can at times affect adolescents and adults as well.

There is a paucity of literature on the clinical profile and cardiac complications of KD from this part of the world. We herein report our experience of KD in children presenting to a tertiary care hospital of our area.

MATERIALS AND METHODS

This was a prospective observational study conducted in the postgraduate department of pediatrics from April 2017 to March 2020. The study group included all the children up to the age of 10 years who met guidelines given by the American Heart Association (AHA).[1,7] After detail history and clinical examination of each patient, the following investigations were carried out-complete blood count, ESR (erythrocyte sedimentation rate, CRP(C reactive protein), urine routine, biochemistry (urea, creatinine, liver function tests), chest radiography, electrocardiogram (depending on clinical requirement) along with indepth cardiovascular assessment.

Cardiovascular assessment

Cardiovascular complications, including coronary artery lesions, were assessed during the acute phase and during the follow-up at three different periods of time (2 weeks, 6 weeks, and 6 months). The coronary involvement (dilatation and small, medium, and giant CAA) was determined by the z-scores adjusted to patients' body surface area (BSA) (Boston formula), if available. We used the z-score stratification proposed by the AHA guidelines (2017) to determine the degree of coronary involvement.[7]

The use of 128-slice dual-source computed tomography coronary angiography was performed in select patients who had large or unusual CAAs or where the visualization of coronaries was difficult.[8]

Patients were managed using standard treatment guidelines as given by the AHA.[1,7] Intravenous immunoglobulin (IVIG – 2 g/kg) given over 10–12 h was used as first-line therapy, along with oral aspirin (initially in anti-inflammatory doses [30–50 mg/kg/day] followed by antiplatelet doses [3–5 mg/kg/day]). Adjunctive therapy (corticosteroids) was used in two patients with IVIG resistance who continued to remain febrile after receiving complete dose of IVIG.

Statistical analysis

Categorical data were expressed as absolute number and percentage. A comparison was made for all parameters between compete KD and incomplete KD as well as whole group. The data presented on categorical scale were compared between the groups with the help of Fisher's exact test. The level of significance was set at 5%, and $P < 0.05$ was considered statistically significant.

RESULTS

Gender distribution, age at the time of diagnosis, and seasonal variations are shown in Table 1. Among 31 patients with KD, the male:female ratio was 2.8:1. The majority of the patients were in the age group of 1–5 years (67.7%). Clustering of cases was seen during the winter months (45.2%). Nineteen (61.3%) fulfilled the criteria of complete KD and 12 (38.7%) were diagnosed as incomplete KD.

Clinical signs of patients with KD, complete and incomplete, are depicted in Table 2. All of the patients (100%) with KD presented with persistent fever of more than 5 days, followed by polymorphous skin rash and oral mucosal changes (87.1% and 83.9%, respectively). Patients with incomplete KD compared with patients with complete KD significantly less presented with oral mucosal changes (58.3% vs. 100%, $P = 0.004$) and changes in extremities (33.3% vs. 78.9%, $P = 0.0072$). Nonclassical symptoms such as arthralgia and gastrointestinal symptoms were present in 29% and 41.9%, respectively.

The analysis of laboratory investigations is shown in Table 3. We found no statistical differences in laboratory investigations between complete and incomplete KD.

Cardiac assessments showed that the majority of the patients with KD (whole group: 54%) had developed coronary artery abnormalities, which was comparatively greater in the incomplete KD group (83.3%) in relation to the complete KD group (36.8%) [Table 4].

Table 5 depicts the time of onset of symptoms to initiation of IVIG. In our study group, the initiation of treatment was within 10 days of onset of symptoms in the majority of the patients 67.7% more so in the patients with complete KD (84.2%) than in the incomplete group (32.2%). This difference in the initiation of treatment between the two groups was statistically significant. Two patients who continued to remain febrile after IVIG received steroid as adjuvant therapy.

The mean follow-up of the patients in our study is 12 months. Children with dilated coronaries were reviewed serially at regular interval of 2 weeks,

Table 1: Demographic characteristic of the patients with Kawasaki disease

	Whole group (*n*=31), *n* (%)	Complete (*n*=19), *n* (%)	Incomplete (*n*=12), *n* (%)	*P*
Gender distribution				
Male	23 (74.2)	13 (68.42)	10 (83.33)	-
Female	8 (25.8)	6 (31.5)	2 (16.66)	-
Age at diagnosis (year)				
<1	6 (19.4)	2 (10.5)	4 (33.3)	
1-5	21 (67.7)	14 (73.7)	7 (58.3)	
6-9	4 (12.9)	3 (15.8)	1 (8.3)	
Seasonal variation				
Winter	14 (45.2)	9 (47.4)	5 (41.7)	
Autumn	3 (9.7)	2 (10.5)	1 (8.3)	
Summer	7 (22.6)	3 (15.8)	4 (33.3)	
Spring	7 (22.6)	5 (26.3)	2 (16.7)	

Table 2: Classical and "nonclassical" symptoms in complete and incomplete Kawasaki disease

Classical symptoms	Total (*n*=31), *n* (%)	Complete (*n*=19), *n* (%)	Incomplete (*n*=12), *n* (%)	*P*
Fever persistent for at least 5 days	31 (100)	19 (100)	12 (100)	-
B/L nonpurulent conjunctivitis	25 (80.6)	17 (89.5)	8 (66.7)	0.174
Oral mucosal change	26 (83.9)	19 (100)	7 (58.3)	0.004*
Cervical LAP	10 (32.3)	7 (36.8)	3 (25)	0.697
Changes in extremities	19 (61.3)	15 (78.9)	4 (33.3)	0.0072*
Rash	27 (87.1)	17 (89.5)	10 (83.3)	0.631
Nonclassical				
Arthralgia/arthritis	9 (29)	3 (15.7)	6 (50)	NS
Gastrointestinal symptoms	13 (41.9)	8 (42.1)	5 (41.6)	NS

*Statistically significant difference (*P*<0.05). NS: Not significant, LAP: Lymphadenopathy

Table 3: Laboratory investigations at diagnosis in complete and incomplete Kawasaki disease

	Total (*n*=31), *n* (%)	Complete (*n*=19), *n* (%)	Incomplete (*n*=12), *n* (%)	*P*
Anemia for age	25 (80.6)	15 (78.9)	10 (83.3)	0.763
WBC >15,000 (μ/L)	20 (64.5)	11 (57.9)	9 (75.0)	0.559
Platelet count >4.5 (lakh)	21 (67.7)	12 (63.2)	9 (75.0)	0.769
CRP >3 (mg/dl)	31 (100)	19 (100)	12 (100)	1.00
ESR >40 (mm/h)	22 (71)	12 (92.3)	10 (83.3)	0.424
Albumin <3.5 (g/dl)	20 (64.5)	12 (92.3)	8 (66.7)	0.843
Transaminitis AST/ALT >45 (u/L)	9 (52.6)	5 (38.4)	4 (33.3)	0.07

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 4: Cardiovascular findings

Z score	Total (*n*=31), *n* (%)	Complete (*n*=19), *n* (%)	Incomplete (*n*=12), *n* (%)	*P*
Z score <2 (normal)	14 (45.2)	12 (63.2)	2 (16.7)	
Abnormal coronary	17 (54)	7 (36.8)	10 (83.3)	
Ectasia	2 (6.5)	0	2 (16.7)	0.025*
Small aneurysm	10 (32.3)	6 (31.6)	4 (33.3)	
Medium aneurysm	4 (12.9)	1 (5.3)	3 (25)	
Large aneurysm	1 (3.2)	0	1 (8.3)	

*Statistically significant difference (*P*<0.05)

6 weeks, and then at 6 months. Table 6 depicts the echocardiographic findings at the end of 6-month period in 17 children who had abnormal coronary artery at the time of diagnosis. Out of such 17 children, 6 patients had normal coronary artery (z-score <2) at 6-month follow-up.

DISCUSSION

The epidemiological characteristics, with a majority of patients <5 years of age with predominance of male gender and the seasonal trends, were similar to those reported in studies from other countries.[9,10] In our study, total 31 children were diagnosed with KD from April 2017 to March 2020, out of which 61.3% were complete KD cases and 38.7% were incomplete KD. The occurrence of KD has increased over time, as found in other studies.[11,12] There is a significant increase in number of cases than a study by Bhat *et al.*[13] which was conducted in the same geographical region. A part of this increase may be related to a better diagnosis of KD associated with increased awareness of the disease and an improvement in the imaging modalities. Incomplete KD rates were higher than expected, with 38.7% of the

Table 5: Time of onset of symptom-to-initiation of treatment

Days	Whole group, *n* (%)	Complete (*n*=19), *n* (%)	Incomplete (*n*=12), *n* (%)	*P*
<10	21/31 (67.7)	16/19 (84.2)	5/12 (41.7)	0.021*
>10	10/31 (32.2)	3/19 (15.8)	7/12 (58.3)	

*Statistically significant: *p* value<0.05

Table 6: Follow-up of 6 months

Abnormal coronary artery	At the time of diagnosis	At 6-month follow-up
TCD	2	0
Small aneurysms	10	6
Medium aneurysms	4	4
Large aneurysms	1	1
Total	17	11

TCD: Transient coronary dilatation

incomplete cases compared to 20% in other studies. This difference may be associated with a high index of suspicion of this presentation of the disease at our institution.[10,12]

Fever was present in all of the patients, which is consistent with studies by Akhtar *et al.*[14] On analyzing the frequency of the clinical signs, rash (87.1%) was the most common finding, followed by oral mucosal changes (83.9%) and bilateral conjunctival injection (80.6%), which is comparable to a study by Perrin *et al.*[15] Changes in extremities were present in 61.3% of the cases. The prevalence of periungual desquamation in patients with KD has been reported to vary from 68% to 98%.[16] Change in extremities and oral mucosal changes were more encountered in the complete KD group (78.9%, 100% vs. 33.3%, 58.3%; $P = 0.022$ and 0.004, respectively), and it proved to be statistically significant.

Cervical lymphadenopathy (LAP) is the least consistent feature of KD.[17] In our study, cervical LAP presented only in 32.3%. Abdominal pain, vomiting, diarrhea, and arthralgia were the nonclassical signs, which is similar to what was reported in the previous studies.[18]

In our study, leukocytosis and thrombocytosis were seen in 64.5% and 67% of the cases, respectively, which was consistent with a study by Bhat *et al.*[13] Low platelet count was seen in 2/31 cases (6.4%). ESR and CRP levels are often elevated in KD, and this was confirmed by our study as seen in 71% and 100% of the patients, respectively. Moreover, anemia with low mean corpuscular volume and mean corpuscular hemoglobin concentration (MCHC) was present in 80.6% of the cases which was consistent with a study by Perrin *et al.*[15]

Effect of KD on cardiovascular system is the most significant clinical problem and has been reported in up to 25% of the patients in literature.[19] In our study, CAA was seen in 54.8%, of which 36.8% were in the complete KD group and 83.3% were in the incomplete KD group, and the difference was statistically significant. There are published studies which have shown that incomplete KD is associated with a higher risk of developing coronary abnormalities.[20,21] CAA is significantly high than a study conducted by Bhat *et al.*[13] which showed CAA in only 2%. The cause could be multifactorial; first, we used a z-score in this study, and it has been established that z-score allows for better evaluation of the severity of coronary artery changes by correcting for BSA.[7] Second, better imaging modalities and the use of CT have further improved the assessment of CAA. In our study, patients with an incomplete presentation were found to experience a longer duration of time between symptom onset and diagnosis/treatment as compared to complete KD cases. The data have shown that delayed IVIG administration due to delayed incomplete KD diagnosis increases the risk of developing CAA.[23] In the present study, CAA developed in 83.3% with incomplete KD and in 36.8% with complete KD with a significant *P* value. Our results are in consonance with the findings of previous studies.[22,23]

All the patients were followed regularly, and the patients with dilated coronaries were assessed specifically for the persistence of CAA. In these patients, the echocardiographic findings at the end of 6-month period were noted. Fifty percent of the children with coronary ectasia and small aneurysm had normal coronaries at follow-up of 6 months. This regression rate is comparable with 50%–67% reported in literature.[1]

One case in our study needs special mention, she was a 7-year-old girl presented to us as pyrexia of unknown origin (PUO). On admission, she was febrile and had desquamation of upper extremities and unilateral cervical LAP. LAB parameters showed thrombocytosis, raised ESR and CRP, and anemia with low mean corpuscular hemoglobin and MCHC. Other workups for PUO came out to be normal. We did an echocardiography which showed giant aneurysm of the left anterior descending (LAD) coronary artery. CT angiography as an additional imaging modality was performed which depicts saccular aneurysm of proximal LAD with evidence of ectasia of the proximal left circumflex artery. She became afebrile and responded after IVIG and steroid therapy. Aspirin and warfarin were added as per the AHA protocol, and her repeat echocardiography at 6 weeks did not show any resolution of aneurysm.

CONCLUSION

We found no differences in demographic features, age of onset, and laboratory tests of patients with complete KD and incomplete KD. Change in extremities and oral mucosal changes were more common in the complete KD

group. Incomplete forms of KD presentation often delay diagnosis and hence treatment which leads to increased risk of CAA in them. Increased awareness among pediatricians is key in preventing cardiac morbidity associated with KD. A significant increase in number of cases and CAA as compared to a previous study in the same geographical area is remarkably striking and warrants further studies. Our follow-up results showed persistence of medium and large aneurysms which highlighted the need of continuous medical follow-up by a pediatrician and cardiologist.

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.

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Conflicts of interest

There are no conflicts of interest.

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