LEADING ARTICLE

Presentation and Outcome of Children with Kawasaki Disease: Experience in A Tertiary Care Hospital in Bangladesh

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Abstract

Background: *Kawasaki disease (KD) is an acute difficult-to-diagnose febrile illness in children caused by self limiting vasculitis in medium and small sized arteries.*

Objetive: *This study has been conducted to analyze its presenting symptoms, clinical course, laboratory findings, and therapeutic options in a tertiary hospital in Bangladesh to aid early diagnosis and optimum management.*

Methods: *This is a retrospective study where the medical records of 31 children admitted and diagnosed with Kawasaki Disease (KD) in Evercare Hospital Dhaka between 2009 and 2020, were assessed. Through a structured form, the demographic information, clinical profile, laboratory results, and echocardiographic data were obtained from the hospital records and then entered into a Microsoft Excel sheet. Cleaned and verified data were transferred to SPSS program version 23 and analyzed to obtain descriptive statistics.*

Results: *Out of total 31 patients with KD enrolled, 64.5% of the patients were between six months to five years of age with a median age of three years; 97% had an age below 6 months. Though 68% of patients met all the required criteria for KD, one-third (32%) were diagnosed as incomplete KD with fewer manifestations. Along with high fever in all cases, the most common clinical features were polymorphous rash (90%) and changes in extremities (90%) followed by changes in the lips and oral cavity (77.4%), cervical lymphadenopathy (68%) and conjunctival injection (61%). Common laboratory abnormalities found were anemia (90%), leukocytosis (65%), thrombocytosis especially in the second week (78%), high ESR (100%), and elevated CRP (84%). About 42% of patients had cardiac abnormalities at the onset. Seven children (63.6%) had coronary artery aneurysms (CAA) whereas 18% had coronary dilatations. In subsequent follow-ups, coronary artery changes remained almost the same up to 6-8 weeks. After 3-6 months, 87.5 % of children recovered from cardiac abnormality.*

Conclusion: *A high index of suspicion for KD and an active search for compatible findings in children with unexplained fever can help in early diagnosis. Timely initiation of IVIG treatment is needed to reduce the risk of cardiac complications. Young infants under six months of age need further careful early suspicion and evaluation because of their incomplete presentation and more vulnerability to developing cardiac complications.*

Keywords: *Kawasaki disease, incomplete Kawasaki, intravenous immunoglobulin, coronary artery aneurysm.*

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Introduction

Kawasaki disease, also known as mucocutaneous lymph node syndrome is an acute febrile, systemic vasculitis condition that predominantly affects children under the age of five.[1,2] In the USA, Europe, and Asia, it is now recognized that children of all nationalities can contract illnesses in endemic and epidemic forms. Kawasaki disease has been recorded in all racial and ethnic groups, as well as across the entire pediatric age range, with most patients being under the age of five. Patients less than six months and older than eight years of age are seen infrequently; however, they may be at more risk of coronary artery aneurysms.[1] The etiology of the disease remains unclear. Autoimmunity with a hereditary component is considered to be linked to the illness.[3] The prevalence of KD varies substantially between geographical areas. The incidence rate of KD in children under the age of five varies between 5 -22 per 100,000 in North America, Europe, and Australia.[4] Its Incidence rate is higher in Asia than in the United States and Europe, particularly in Northeast Asia.[5,6] The current KD rate in Japan is 265/100,000 under-five children, which is the highest KD rate ever recorded. By the time they are 10 years old, it is estimated that 1% of Japanese children will have KD. Korea reported an incidence rate of 134.4 (second highest in the world) per 100,000 under-five-year-olds, whereas Taiwan reported an incidence rate of 82.8.[6,8] In East Asian countries KD is considered an endemic disease that mostly appears at 6 months to 4 years of age.[6]

A recurrent fever, frequently 40°C or higher, is typical of the acute phase and typically signals the onset of a disease. The duration of the febrile episodes in children who are left untreated, ranges from 5 to 25 days, with an average duration of approximately 10 days.[9] Bilateral conjunctival injection mainly affects the bulbar conjunctivae, without suppuration, and usually starts soon after fever appears. Bright red, swollen lips with vertical cracking with bleeding were the most recognizable alterations. Bright red oropharyngeal mucosa and a classic "strawberry" tongue are other presentations. In the acute stage of the illness, erythema of the palms and soles is one of the changes in the peripheral extremities. The erythematous rash typically starts on the trunk and progresses to the face, extremities, and perineum during the acute phase of the illness, which can last between one or two days and a week or more. Cervical lymphadenopathy is the least common clinical feature among KD patients.[1] Some children with KD do not meet all the traditional criteria for clinical diagnosis. Children with fever, and fewer than four of the other symptoms of the disease have atypical or incomplete KD. Atypical KD is also more prevalent among young children and identifying this variation can be challenging; they are also at higher risk of developing coronary artery aneurysms (CAA), with fatal consequences.[10] Cardiovascular involvements are the major cause of long-term morbidity and death in the acute phase of Kawasaki disease.[1]

In Bangladesh, the Kawasaki disease is underreported owing to a lack of widespread public knowledge. However, the scarcity of data has led to an enormous research gap. The purpose of this was to assess the features, presenting symptoms, diagnostic criteria, laboratory testing, and treatment of Kawasaki disease (KD) in children identified and treated at a tertiary hospital in Dhaka, Bangladesh.

Materials and Methods

This retrospective study was conducted over a period of 12 years from 2009 to 2020, in a tertiary care hospital in Dhaka. We have included every hospitalized child with a diagnosis of KD or IKD, ranging in age from 3 months to 13 years, as study subjects. Both complete and incomplete KD was diagnosed according to the American Heart Association (AHA) guidelines (Table I). [11]

Table I
Diagnosis of Classic KD and IKD

Fever for five days and at least four of the key clinical symptoms listed below are required for the diagnosis of classic KD.

Changes in extremity: in acute phase erythema of palms, soles; edema of hands and feet while in subacute phase children may experience periungual peeling digits of hand and feet.

Polymorphus exanthem: Rash maculopapular, diffuse erythroderma, or erythema multiforme-like Bilateral bulbar conjunctival injection without exudate

Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae

Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral

When coronary artery anomalies are discovered by 2-D echocardiography or angiography in patients with fever for at least 5 days and 4 major criteria, Kawasaki disease can be diagnosed.

Incomplete Kawasaki disease (IKD) should be evaluated in all children who have an unexplained fever for 5 days and two or three of the main clinical characteristics of Kawasaki disease.

Data on the patient's demographics, clinical profile, laboratory results, echocardiographic findings, and comprehensive drug list were gathered from hospital records and organized in an Excel spreadsheet with prior consent from the institutional ethical review committee of Evercare Hospital. At admission, all children underwent tests for complete blood count (CBC), CRP, erythrocyte sedimentation rates (ESR), serum electrolyte profiles, and liver enzymes. Echocardiography was performed at diagnosis, at 2-4 weeks, 6-8 weeks, and at 3-6 months of diagnosis. When the Z score is greater than 2.5, a coronary artery aneurysm (CAA) was diagnosed in the case of arterial dilatations with more than 2.5 Z scores, whereas Z scores of 2 to 2.5 were taken as coronary dilatations. Different therapeutic agents and regimes used, such as serum IVIG, corticosteroids, antibiotics, and thrombolytics, were noted. Through a structured form, demographic information, clinical profile, laboratory results, echocardiographic data, and therapeutic agents obtained from the hospital records were entered into a Microsoft Excel sheet. Cleaned and verified data were transferred to SPSS program version 23 and analyzed to obtain descriptive statistics. Data were presented in tabular form with mean, standard deviation, proportion, and range as appropriate.

Results

Out of the 31 admitted children, 58% were male. Almost two-thirds (65%) of them were 6 months to 5 years age. Over one-fourth of children were aged more than 5 years at the time of admission. All the children were admitted with fever, and almost 80% of them presented within 7 days of fever onset. Along with fever, 90% of children had a polymorphous rash and changes in extremities, while other prominent clinical manifestations were changes in lips and oral cavity (77.4%), cervical lymphadenitis (68%), conjunctivital injection (61.3%), respiratory symptoms (42%), extreme irritability (39%) and abdominal complaints (36%). Besides, in a few cases arthritis, BCG scar reactivation, and urticaria were also noted (Table II).

About 65% of children presented with 3 to 4 criteria on admission. Among 31 children, twenty-one (67.7%) patients were classified as having complete KD while the rest (32.3%) were patients with incomplete KD. In typical KD group, no patient was found below 6 months of age; 62% of patients in this group were aged 6 months to 5 years group. On the other hand, in the incomplete KD group, none were more than 5 years old; 30% of children in this group were below 6 months of age (Table III).

Table II

Distribution of patients by their demographic and clinical characteristics (N = 31)

Patient's characteristics	Results N(%)
Sex	
Male	58
Female	42
Female: Male	1:1.38
Age category (%)	
<6 months	3(9.7)
6 months - 5 years	20(64.5)
>5 years	8 (25.8)
Total number of fever days before admission to hospital (n, %)	
Fever for ≤7 days	24(77.4)
Fever for > 7 days	7(22.6)
Mean duration of fever (days, range)	5.94 (2-14)
Others	
Polymorphous rash	28(90.3)
Conjunctival Injection	19(61.3)
Changes in extremities	28(90.3)
Lips and oral cavity change	24(77.4)
Cervical lymphadenitis	21(67.7)
Extreme irritability	12(38.7)
Cough and respiratory distress	13(41.9)
Urticaria	3 (9.7)
Arthritis	5(16.1)
Erythema and induration at BCG inoculation site	2(6.5)
Abdominal complaints (Abdominal pain, vomiting, loose motion)	11(35.5)

Table III

Distribution of patients by number of criteria fulfilled and by category of disease characteristics

KD criteria fulfilled	On admission n(%)	On final diagnosis n(%)
1-2 KD criteria fulfilled	5(16.1)	2(6.5)
3-4 KD criteria fulfilled	20(64.5)	21(67.7)
5 KD criteria fulfilled	6(19.4)	8(25.8)
Age group	Kawasaki Disease	Incomplete KD
<06 months se category	0	3/10(30)
6 months – 05 years wasaki Disease	13(61.9)	7(70) 1(67.7)
>05 yrs	8(38.1)	100 (32.3)

Results of Laboratory investigations show a high frequency of anaemia, high leukocyte count, raised ESR, highly elevated CRP, and high SGPT. Mean Haemoglobin was 9.5 gm/dl, and a vast majority (90%) had anemia. Leukocytosis was found in 87% of the children on admission. Typically, a majority (78%) developed thrombocytosis in the second week of illness. All had raised ESR. Out of 31 children, 26 of them (84%) had a high CRP on admission. Almost half of the children had raised SGPT. Hypoalbuminaemia, hyponatremia and sterile pyuria were other important laboratory findings in our affected children (Table IV).

Table IV

Distribution of patients by laboratory findings

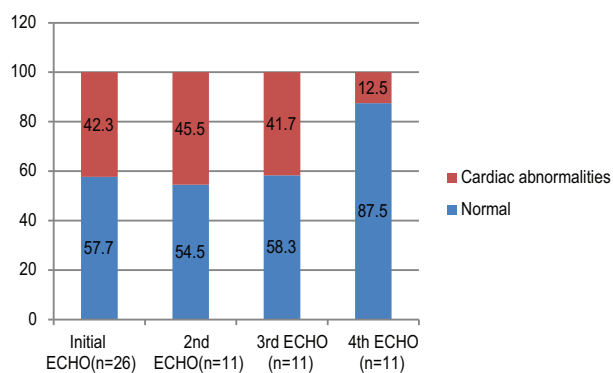| Characteristics	Results
Hemoglobin mean ± SD, maximum and minimum Anemia (<11gm/dl), n(%)	9.56 gm/dl ± 1.1; 11.7 & 6.8 28(90.1)
Leukocyte count on admission mean ± SD,:maximum and minimum Leukocytosis (≥11,000/μL), n(%)	18988.4±8314.6; 40000 & 6800 27(87.1)
Leukocyte count on admission mean ± SD,:maximum and minimum Leukocytosis (≥11,000/μL) on diagnosis n(%)	15901.4±8314.6; 41900 & 4500 21(76.0)
Platelet count mean ± SD,:maximum and minimum Thrombocytosis (≥450×103/μL) on admission, n(%)	$594.1×10^3 ±236.5; 815×10^3$ & $225×10^3$10/31 (32.3)
Platelet count mean ± SD,:maximum and minimum Thrombocytosis (≥450×103/μL) on diagnosis, n(%)	$434.5×10^3 ±147.7; 1442×10^3$ & $246×10^3$24(77.7)
ESR mean ± SD,:maximum and minimum Raised ESR (>10mm/hr)	76.8 ±24.4; 130 & 23 28(100)
Raised CRP mean ± SD,:maximum and minimum Raised CRP (C-reactive protein) (>3 mg/L)	10.0±7.6; 37& 0 26(83.9)
SGPT mean ± SD,:maximum and minimum Raised SGPT (>45 IU/L)	76.1±89.6;418 &12 14(45.2)
Serum sodium level(mmol/l) Na+ level < 135, n(%) Na level ≥135, n(%)	10(47.6) 11(52.4)
Serum albumin (gm/L) <2.5gm/dl, n(%) 2.5-3.5gm/dl, n(%) >3.5gm/dl, n(%)	7(26) 17(63) 3(11.1)
Sterile pyuria	7(22.6)

Fig.-1 *Timing of echocardiography (Initial - by 7-10 days of onset of illness, 2nd - at 2-4 weeks follow up, 3rd - at 6-8 weeks follow up, 4th - at 3-6 month follow up. Y axis shows % of children)*

Figure 1 shows the proportion of patients with echocardiographic abnormalities at different timelines of the disease. The procedure could not be done in all cases for compliance issues. +Findings were grouped in four points in the timeline: the initial one was done within 7-10 days of symptom appearance, second, third, and fourth ones were done at 2-4 weeks, 6-8 weeks and 3-6 months follow up respectively. Initial echocardiography showed cardiac abnormalities in about 42% of cases. In subsequent follow-ups, this proportion remained almost the same. After 3-6 months, 87.5 % of children recovered from cardiac abnormality. Initial echocardiography showed abnormality in 11 patients (42.3%); out of them, 7 children (63.6%) had coronary artery aneurysms (CAA), whereas 2(18%) showed coronary dilatations, 1 patient had pericardial effusion and 1 had heart failure. Repeated echocardiograms taken up to four years later, revealed full recovery in one child who had persisting coronary abnormality during six months follow up.

Table V

Distribution of patients by specific therapeutics used

Therapeutics used	Frequency (%)
IVIG administered to n(%)	27(84.0)
Day of IVIG administration, mean ± SD; range	9.2±2.3: 7-15
IV-IG administration within 10 days of onset	20(74.1)
IV-IG administration after 10 days of onset	07(24.9)
Aspirin given to n(%)	26(83.9)
High dose aspirin (100 mg/Kg)	21(80.8)
Medium dose aspirin (30 mg/Kg)	5(19.2)
Prednisolone to n(%)	2(6.4)
High dose Inj. Methyl Prednisolone (20 mg/kg/d) for 4 days	1(3.2)
Oral Prednisolone (2 mg/kg/ day) for 10 weeks	1(3.2)

According to Table V, out of 31 patients, twenty-seven (84%) received IVIG; and the parents of five children refused it. One received high dose Inj. Methyl Prednisolone. Those who got IVIG happened to receive it within 7-15 days of the onset of the disease. Twenty children (74%) received it within 10 days of symptom onset. Twenty-eight patients (90%) were given Aspirin, and 21 of them (81%) got a high dose of 100 mg/Kg/day. Only one child received oral Prednisolone at home for 10 weeks along with low dose Aspirin.

Children who performed additional imaging Checkups over a period of 2-4 weeks revealed that 5 of the 10 children who received IV immunoglobins before 10 days experienced cardiac abnormalities. At the 6- to 8-week checkup, 4 of the 5 children who had cardiac abnormalities received immunoglobin within 10 days. It was further demonstrated that 88% of kids had no cardiac abnormalities after 3-6 months of follow-up. Only one child who received immunoglobin after 10 days continued to demonstrate cardiac abnormality. Poor number of follow up echo cannot support or refute any association between cardiac anomaly and IVIG.

Discussion

KD is the most frequent systemic vasculitis in children.[12] The incidence of KD is still unknown in many underdeveloped countries due to overlapping features with other childhood illnesses, lack of awareness among physicians, and sub-optimal or non-existent nationwide surveillance.[7,13] Children from East Asia or with Asian heritage who reside elsewhere in the world have the highest prevalence of KD due to their Asian ethnicity.[7] In Bangladesh, the incidence of KD is still unknown.[14]

Kawasaki disease can present in two ways. Our study shows that 68% and 32% of children presented as typical and incomplete KD respectively, which is consistent with other study findings.[15-16] Kawasaki disease is most prevalent among 6 months to 05 years of age group [16], and our study also supports this data, though in Barron's in study, aging pattern was slightly different where about 80% of children were of 6 months to 4 years of age.[17] Increasing occurrence in children between the ages of 6 months and 5 years old may be related to immaturity of the immune system in this group, and those below 6 months being protected by mother's antibody through placenta and breast milk.[18] Younger infants present with fewer criteria leading to the diagnosis of Incomplete Kawasaki disease (IKD).[19] According to some of the previous studies, this accounts for about 15-20% of all cases occurring less than 1 year of age.[12-19] In our study, we found all patients below 6 months of age presented as IKD, which is 30% of all IKD patients. As per sex is concerned, we found some male preponderance at male female ration of 1.38: 1, which corresponds with other studies.[20-21]

In this study, we have described clinical features along with laboratory findings in patients with KD. In various studies the most frequent diagnostic symptoms were persistent fever and peripheral

desquamation, while cervical lymphadenopathy is the least frequently found.[22,23] This finding is identical to our study except cervical lymphadenopathy. No biomarker has been identified so far that can be used to diagnose KD with complete conviction. As it is an inflammatory disease, CRP is usually very high, ESR, Leukocytes and Liver enzymes are raised. Anaemia, thrombocytosis, hypoalbuminemia, hyponatremia and sterile pyuria also support the diagnosis of KD.[24,25] In this research, 90% of admitted children suffered from anemia, and the finding also matches with other studies.[26] We have found most of the children to have thrombocytosis on the second week of follow-up. This feature has regularly been documented in the second to the third week of the disease in patients with KD.[27,28] It was once believed to be a benign reactive phenomenon due to underlying inflammation. Recent discoveries in platelet biology, however, seem to indicate that platelets are becoming more active as well as more numerous, which raises the risk of thrombosis.[28,29]

The preferred diagnostic technique for detecting coronary artery anomalies and evaluating myocardial function in Kawasaki disease is echocardiography. Also, it aids in the classification and risk assessment of KD patients.[29] The fundamental reason for fatalities in Kawasaki disease is the involvement of the myocardium and coronary arteries.[8] In our study, an echo performed in the acute stage of the disease showed that 11(42.2%) children suffered from various forms of cardiac abnormalities although 9(81.9%) of them had IVIG within 10 days of onset. Additionally, 7 (64%) out of those 11 patients had coronary artery aneurysms and 05 of them received IVIG within 10 days. Three of the three infants under six months old had cardiac abnormalities, even though immunoglobin had been given to two of them within 10 days. More common cardiac abnormalities in younger infants may be due to incomplete presentation thus leading to a delay in diagnosis. This finding is consistent with many prior studies.[19,30-32]

IVIG is thought to lower the incidence of coronary artery lesion through controlling the immune system, which includes modulating cytokine production, neutralizing bacterial super antigens or other causative factors, and suppressing endothelial cell activation.[33] According to the 2004 American Heart Association (AHA) guidelines for KD, IVIG should be administered no later than 10 days following the beginning of the illness and, if at all feasible, no later than 7 days. Our research, on the other hand, showed that early immunoglobin treatment (before 10 days) failed to cease the development of cardiac abnormalities in second and third follow up, while there is evidence that it might serve as a protective factor against the onset of coronary lesions. Limited data, ethnicity, severity of disease, KD features, and treatment resistance could be the potential contributors to this conclusion.[33] However, over the time only one child continued to show cardiac abnormality up to 6months and rest of the cases were resolved within this period. Hence, it is evident that immunoglobin prevents long term cardiac complications by reducing hyperinflammation.[33-35] Regarding use of Aspirin, in our study, we used high dose (100 mg/Kg) during acute febrile phase of the disease for initial period. In our study, 68% of children received high doses of aspirin. However, it was reported that high-dose aspirin did not affect the IVIG response rate, fever duration, or coronary artery lesion incidence in the acute phase of the disease.[36] In later part of treating KD patients, we have used medium dose of 30 mg/Kg per day for acute phase inflammation, thus reducing the side effect. Ultimately, it is documented that effective early treatment the incidence of coronary artery aneurysms from 20% to 5% while also reducing acute symptoms.[37]

Conclusion

This study done in a South-East Asian setting, reconfirms the clinical features, laboratory findings and disease course with standard management. This emphasizes the importance of high index of suspicion in dealing with readily unexplained high fever in children to search for compatible signs and laboratory findings. Infants below 6 months or 1 year of age with reduced number of clinical criteria need extra care to diagnose. Early diagnosis and early effective management, and longtime periodic cardiac follow up is paramount to control hyper inflammation and avoid long term cardiac abnormalities.

Recommendation

Although the present study has brought forth interesting findings about KD in an Asian community, reconfirming previous findings in this setting, a cohort with a larger sample can give more

confidence. More extensive follow-up data with minimum dropouts will be valuable to reveal long-term cardiac outcomes.

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