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"Clinical Profile and Outcome and Risk Factors of Cardiovascular Involvement in Hospitalized Children with Kawasaki Disease"

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ABSTRACT
Kawasaki disease (KD), also known as Kawasaki syndrome, is an acute febrile illness of unknown cause that primarily affects children younger than 5 years of age.The present study was conducted to study the clinical profile and outcome and risk factors of Kawasaki disease in children. This observational prospective study was conducted in cardiology ward with a diagnosis of Kawasaki disease from 1st June 2020 to 31 July 2021 in Bangabandhu Sheikh Mujib Medical University Hospital Dhaka, Bangladesh. Forty five (45) children aged between 3 months to 10 years were studied. Kawasaki disease is more prevalent among male child (73.33%). Most commonly encountered risk factor for cardiovascular involvement especially coronary dilatation or aneurysmal change is more observed in younger age of presentation. Fever, rash, conjunctivitis, erythema and edema of limbs, periungual skin desquamations are the presenting features. Cardiovascular involvement of left main coronary artery dilation is the most frequently observed aneurismal change observed among study population which was evident in 68% of the children having coronary involvement. All the study patient received high dose aspirin (100%) and 93% received IVIG of whom 6.66% had IVIG- resistant Kawasaki disease. Commonly occurring complication is uveitis (17.77%). Among the total 45 study population 1 patient expired (2.22%).Clinicians should have a high index of suspicion of Kawasaki disease in persistently febrile patients and once clinically diagnosed, echocardiography should be done and IVIG therapy along with aspirin should be started, specially in infants (<6 months) as they have the higher tendency to develop coronary aneurysm.

Keywords: Characteristics, Cardiovascular Involvement, Aneurysm, IVIG, Treatment, Outcome.

I. INTRODUCTION

Kawasaki disease (KD), also known as Kawasaki syndrome, is an acute febrile illness of unknown cause that primarily affects children younger than 5 years of age.[1] The disease was first described in Japan by Tomisaku Kawasaki in 1967, and the first cases outside of Japan were reported in Hawaii in 1976.[2] Clinical signs include fever, rash, swelling of the hands and feet, irritation and redness of the whites of the eyes, swollen lymph glands in the neck, and irritation and inflammation of the mouth, lips, and throat.The disease usually occurs in infants and children under 5 years.[3,4]Although one or more infectious triggers are most likely, the precise etiology is still unknown. There is no specific diagnostic test or pathognomonic clinical feature and still diagnosis of KD is made on clinical criteria.[5]Children with Kawasaki disease might have high fever, swollen hands and feet with skin peeling, and red eyes and tongue. But Kawasaki disease is usually treatable, and most children recover without serious problems if they receive treatment within 10 days of onset.The diagnostic criteria includes simultaneous presence of high grade fever for 5 or more days with at least 4 out of 5 symptoms (bilateral non-exudative bulbar conjunctivitis, polymorphous exanthema, erythema of lips and oral cavity, edema

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and desquamation of extremities and cervical lymphadenopathy) or fever associated with less than 4 of the diagnostic criteria and echocardiographic abnormalities of the coronary arteries.[6] Other manifestations like arthritis or arthralgia, diarrhea, vomiting, abdominal pain, irritability, aseptic meningitis, aseptic pyuriaetc may be present.[7] In children younger than 6 months, the diagnosis of Kawasaki disease is quite difficult as the presentation is usually atypical or not fulfilling the clinical criteria and it accounts 15-20% of all patient.[8] Therefore, a high index of suspicion is needed foranyinfantorchildwithfever ofunknownorigin,inorderto avoidamissedordelayeddiagnosis.

II. MATERIALS AND METHODS

This study is an observational prospective study. This observational prospective study was conducted in cardiology ward with a diagnosis of Kawasaki disease from 1st June 2020 to 31 July 2021 in Bangabandhu Sheikh Mujib Medical University Hospital Dhaka, Bangladesh. The diagnosis of KD was made when a child of any age- group presented with unexplained fever (>38° C) for at least five days and four of the following: (i) bilateralconjunctival congestion without exudate, (ii) changes of the oral mucous membrane (any 1): congested pharynx, congested/fissured lips, strawberry tongue, (iii) Polymorphous rash, (iv) changes of the extremities: desquamation or edema, and (v) unilateral lymphadenopathy[9]. Demographic data and base-line characteristics were collected and a structured history was taken. Baseline laboratory work-up included hemoglobin, white cell counts, and inflammatory markers like CRP and/or ESR and transthoracic echocardiography (TTE) using Vivid E9. Parasternal long- and short-axis windows, as well as apical four- and two-chamber views, were used to obtain two-dimensional evaluations, M-mode dimensions and duplex Doppler studies. Additional tests like urine microscopy, urine/blood culture, renal and liver function test were done based on clinical circumstances. Specific attention was paid to potential risk factors. During the physical examination, the presence or absence of any vascular phenomena was also sought.Upon diagnosis, patients received intravenous immunoglobulin (IVIG) (2 g/kg) infused over 10-12 hours and oral aspirin (80 mg100mg/kg/d). IVIG-resistant KDwas defined as persistent or recrudescent fever 36 hours after the completion of the initial immunoglobulin infusion. Data were analyzed using SPSS software version19.

III. RESULTS

Table I: Sex and Age distribution of the study patients (n=45)

Sex	N	%
Male	33	73.3
Female	12	26.7
Age		
>6months	4(M-3;F-1)	8.88%
6months-<1yr	3(M-3;F-0)	6.6%
1yr-<2yr	10(M-8;F-2)	22.22%
2yr-<3yr	8(M-6;F-2)	17.77%
3yr-<4yr	4(M-4;F-0)	8.88%
4yr-<5yr	4(M-2;F-2)	8.88%
5yr-<7yr	5(M-3;F-2)	11.11%
7yr-<9yr	4(M-2;F-2)	8.88%
>9yr	3(M-2;F-1)	6.6%

In this study out of total 45 study population 73.3 %(n=33) were male and 26.7 %(n=12) were female. Mean patient age was 3yr-<4yr (range, 3months to 10 years), and 4(8.88%) patients were <6 months of age, 3(6.6%)patientswerebetween6monthto<1yearand>9 yearsrespectively,10(22.22%)patientswere1yearsto < 2 yrs., 8(17.77%) are between 2 to 3yrs, 4(8.88%) were respectively between 3 to 4 years and 4 to 5 years and between 7 to 9 years, 5(11.11%) between 5 to 7 yrs. of age (Table-1).

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Table-2: Distribution of provisional/referral diagnosis (n=45)

Initial diagnosis	n	%
Suspected Leukemia	2	4.44
Pyrexia of unknown origin	19	42.22
Heart failure	3	6.66
Enteric fever	6	13.33
Septicemia	10	22.22
Hepatitis	3	6.66
Meningitis	1	2.22

None of the under six month patients were neonates. The trend is gradual increment in the number of diagnosed patients of Kawasaki disease every year. This study shows provisional or referral diagnosis of 42.22 %(n=19) were Pyrexia of unknown origin and enteric fever 13.33 %(n=6). The other provisional diagnoses are septicemia 22.22% (n=10), heart failure and hepatitis both 6.66 %(n=3), suspected leukemia 4.44 %(n=2) and meningitis 2.22 %(n=1) (Table-2).

Table-3: Presenting features of the patient (multiple response) (n=45)

Presenting feature	n	%
Fever(>5 days)	45	100
Skin rash (polymorphous)	26	57.77
Non purulent conjunctivitis	44	97.7
Changes in the lips and oral cavity(lip cracking, strawberry tongue, erythema)	43	95.5
Erythema of palms and soles	37	82.22
Edema of hands and feet	36	80.0
Periungual peeling	32	71.11
Perianal desquamation	35	77.77
Cervical lymphadenopathy(unilateral, >1.5cm)	23	51.11
Hepatomegaly	5	11.11
Arthritis/arthralgia	6	13.33
Asceptic meningitis	1	2.22
Uveitis	7	15.55
Pyuria(sterile)	4	8.88
Mean duration of fever 12±3 days		

This study also shows all the 45 patients (100%) had fever. They also presented with conjunctivitis (97.7%),changes in oral mucosa (95.5%), erythema of palm and soles (82.22%), edema of hand and feet (80.0%), perianal desquamation(77.77%) and periungual peeling of skin(71.11%).The other presentations were cervical lymphadenopathy(51.11%), skin rash(57.77%), arthritis, uveitis, hepatomegaly, sterile pyuria and aseptic meningitis (Table-3).

Table-4: Distribution of Laboratory data (multiple response) (n=45)

Laboratory data	Frequency	Percentage
Anaemia	30	66.66%
Leukocytosis(WBC count>15,000/mm^3)	35	77.77%
Neutrophils (%) (>70%)	40	88.8%
Thrombocytosis(Platelet count>450000/$mm^{3)}$	31	72%
Raised ESR(>50mm/h)	39	86.66%
Raised CRP(>6 mg/dL)	33	76.7%
Blood culture positive	1	2.2%
S. ALT(>45U/L)	20	44.44%
Raised S.creatinine(>100µmol/L)	1	2.2%
Abnormal Lipid profile	2	4.44%

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In this study majority of patients had neutrophilic leukocytosis (n=40 0r 88.88%), raised ESR (n=39or 86.66%). Raised CRP and leukocytosis were found in 77.77% (n=35). Anemia was observed in 66.66% patient. Positive blood culture and raised serum creatinine was found in 2.2% of patients respectively; 4.44% patient (n=2) had abnormal lipid profile (Table-4).

Table-5: Distribution of echocardiographic data (multiple response) (n=45)

Echocardiography findings	Artery involved	No of cases (%) (n=19)	Mean Size (mm)
Change in artery or aneurysms	Left main coronary artery (LMCA)	68%(N=13)	2.9 ± 0.47
	Left anterior descending artery (LAD)	52%(n=10)	2.8 ± 0.43
	Left circumflex artery (LCX)	10.5%(n=2)	2.2 ± 0.11
	Right coronary artery (RCA)	36.8%(n=7)	3.2 ± 0.41
	Both LAD and LCX	15.7%(n=3)	3.0 ± 0.32
	LMCA, LAD, LCX and RCA	10.5%(n=2)	3.1 ± 0.21

Table-6: Distribution of other echocardiographic findings (multiple response) (n=45)

Other echocardiography findings	No of cases(n=19)
Pericardial effusion	6
LV dysfunction	3
Mitral regurgitation	2
Tricuspid regurgitation	2

Echocardiographic evaluation shows among the 19 patients having coronary change majority that is 68% had isolated left main coronary artery (LMCA) dilatation with mean size 2.9±0.47 (mm). Second highest range of dilatation was observed in right coronary artery (RCA) with mean size of dilatation 3.2±0.41 (mm). Both LAD and LCX dilatation was found in15.7% children with mean size of 3.0±0.32 (mm). All 4 coronary vessels (LMCA, LAD, LCX and RCA) were found dilated in 2 patient (10.5%). Other than coronary dilatation, 6 patient out of 19 patients had pericardial effusion, 3 had left ventricular dysfunction and 2 patient each had mitral regurgitation and tricuspid regurgitation (Table-5,6).

Table-7: Treatment options (n=45)

Treatment	n	%
Intravenous immunoglobulin(IVIG)	42	93%
Requiring second dose of IVIG	3	6.9%
High dose Aspirin(80-100mg/kg) in acute phase	45	100%
Antiplatelet drug(Clopedogril)	2	4.44%
Anti-coagulant(Warfarin)	5	11.11%
20% human albumin	1	2.22%

This study shows treatment received by the patients of this study. Out of 45 of the study patient, 42 patient (93%) received at least single dose of IVIG @ 2gm/kg over the period of 10-12 hours. 65% 0f patient received IVIG within 12 days of onset of fever and rest of the patient, that is 35% patient received IVIG after this period. Among the three patients who did not received IVIG, two patient left hospitalagainstmedicaladvice(LAMA)andonepatien texpired.Againoutofthe40patientwhoreceived initial dose of IVIG required 2nd dose of IVIG due to recurrence of fever or IVIG resistant KD after 36 hours after initial IVIG therapy (Table-7). All the 45 study patient received high dose of aspirin(80-100mg/kg/day) in the initial stage and was switched to lower dose (3-5mg/kg/day) for only antiplatelet activity for 6 weeks or longer. However 5(11.11%) patient required anticoagulant drug that is warfarin. Two patient were given additional

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antiplatelet agent as clopedogril and one patient required 20% human albumin infusion (Table-7).

Table-8: Complications and outcome (n=45)

		n	%
Complications	IVIG resistant Kawasaki	3	6.66%
	Acute kidney injury	1	2.22%
	Hepatitis	4	8.88%
	Uveitis	7	15.55%
	Asceptic meningitis	1	2.22%
	Convulsion	2	4.44%
	Hearing loss	1	2.22%
Outcome	Improved	39	86%
	Requiring second dose of IVIg	3	6.66%
	Discharged against medical advice	2	4.44%
	Died	1	2.22%

The complications observed in the study populations were recurrent Kawasaki in 3(6.66%) patient, acute kidney injury in 1 (2.22%) patient, uveitis in 7(15.55%), Hepatitis in 4(9.3%), convulsion in 2(4.6%) and 1(2.3%) patient each experienced aseptic meningitis and hearing loss. Regarding outcome of the patient 39 patient (86%) were improved. Two patient (4.44%) left against medical advice and one patientdied (Table-8).

IV. DISCUSSION

Kawasaki disease (KD) is an acute vasculitis of childhood with a special predilection to involve coronary arteries. If untreated, it can lead to coronary artery aneurysms in 25% of cases.[10]It was previously called mucocutaneous lymph node syndrome and infantile periarteritisnodosa.[11]In countries like Japan, the United States, and certain European countries, KD is now considered as the most common acquired heart disease in children.[11]Kawasaki disease is an acute multisystem vasculitis of unknown etiology that occurs in children of all races, but is more common in Japan (up to 175 per 100,000).[10] The incidence of Kawasaki disease is increasing worldwide.[12] It has surpassed rheumatic fever as the leading cause of acquired heart disease in children according to some studies.[13]This may be males are more prone to develop Kawasaki disease or may be because socially females are still neglected while seeking healthcare even in serious health issues in perspective of Bangladesh. In Japanese children, the incidence of KD is highest between 6 and 12 months of age but in our study highest incidence of Kawasaki disease was observed among children of 1 to 2years of age (20.68%).In this study all of the study patients (n=45 or 100%) presented with fever with mean duration was 12±3 days. In studies by Akhtar et al and Singh et al fever was present in 100% of the patients. Non purulent conjunctivitis (97%) was the second most commonly observed symptoms in this study. In a study by sayeed et al 100% of patient had bilateral conjunctivitis and Burns et al shows 70% patient had anterior uveitis. In this study unilateral cervical lymphadenopathy (51%) was the least observed feature which was set as one of the cardinal feature for diagnosing Kawasaki disease and it is similar to the study by Sayeed et al where lymphadenopathy was found only in 68%. The causative agent still remains unclear.[14] No study addressing cardiovascular involvement in Kawasaki disease among pediatric age group has been published from Bangladesh.According to some international studies, males are generally affected more from KD than the females.[15-16]Another study from India showed that KD is definitely being increasingly recognized and reported in India.[18] This could be either due to an actual rise in number of cases or due to increased awareness amongst pediatricians.Many physicians and pediatricians are of the view that rise in KD coincided with the fall of incidence of diarrhea and better vaccination coveragerates.[19] A study 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.[17] In this study it is also observed that male child are more affected (72%) by Kawasaki disease. However, in the USA and Europe, the peak age group for KD is 18-24 months.[19]In Kawasaki disease, fever occurs because of the elevated levels of different proinflammatory cytokines, which are also thought to mediate the underlying vascular inflammation affecting the cardiovascular system. Cardiac involvement is the most important feature

of Kawasaki disease. Cardiac involvement has been variably reported in up to 25% of the cases and coronary artery involvement was seen in 41%ofourcases.[20]Inthisstudy42.22%ofthepatients(n =19)showedfeaturesofcoronaryinvolvement.
Involvement of the left main coronary artery (LMCA) was most observed coronary change found in 68% with mean size 2.9±0.47mm and least was left circumflex artery (LCX) change (10.5%) of patients having coronary change. A study by Saleem et al also showed left main coronary artery, left anterior descending coronary artery and right coronary artery are more likely to be involved and circumflex branch is least commonly involved which is more or like consistent with our present study. Furusho et al described the role of IVIG treatment which became standard of care. The benefits of higher doses of IVIG with aspirin was demonstrated in a review of 1629 patients with KD from six randomized controlled studies.[21] In this study also 93% of the patient received intravenous immunoglobulin and 100% patient high dose of aspirin in acute phase. The commonly observed complication was uveitis observed in 17.77% (n=45) and 6.66% patient had IVIG resistant Kawasaki disease. A study conducted by Choi et al in Korea also revealed uveitis as common complication and most important criteria for diagnosing Kawasaki disease. As for many physicians in developing countries like Bangladesh, where the burden of infectious disease is high, KD is still not commonly included in the differential diagnosis of children presenting with fever. Some of the cardinal manifestations of KD (e.g., fever, rash and lymphadenitis) are also seen in many pediatric infectious diseases and it is not surprising that KD gets overlooked in such a milieu. Therefore, pediatricians in developing countries need to be sensitized aboutKD.

V. CONCLUSION AND RECOMMENDATION

Kawasaki disease is now fast emerging as one of the important cause of acquired heart disease and significant contributory factor to the long-term cardiac morbidity and mortality in these patients. Therefore, clinicians should have a high index of suspicion of Kawasaki disease in persistently febrile patients and once clinically diagnosed, echocardiography should be done and IVIG therapy along with aspirin should be started, especially in infants (<6 months) as they have the higher tendency to develop coronary aneurysm. Authors are recommending multi-centre study with large sample size.

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