Original Article

Coronary Artery Involvement in Kawasaki Disease-Echocardiographic Evaluation of Cases in a Tertiary Care Hospital

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Abstract:

Key Words: Diabe

Background: Kawasaki disease (KD) is the leading cause of childhood acquired heart disease. Cardiovascular manifestations can be prominent in the acute phase of the illness. Echocardiography is useful in recognizing these cardiac manifestations. We carried out a retrospective study by analyzing the data of Kawasaki disease patients in a tertiary care hospital.

Methods: The prevalence of coronary artery dilatation and clinical outcome were documented. Clinical, laboratory, and echocardiographic findings were obtained at baseline and 1 week, 6 weeks after initial therapy with intravenous immunoglobulin in addition to high doses of Aspirin which reduces the risk of coronary artery aneurysm.

Results: One hundred and forty-nine patients with mean age 3± 2 years old, 60% males with Kawasaki disease were included. One hundred and thirty-two patients had coronary involvement (left main coronary artery 36.37 %, left anterior descending artery 28.03%, right main coronary artery 24.25%, circumflex branch in 11.37%). Administration of intravenous immunoglobulin (IVIG) and aspirin has greatly reduced the incidence of coronary lesions in affected children. The initial cardiac findings developed over first few weeks of illness resolved in most of the cases in the subsequent echocardiogram studies after IVIG. The mean duration to normalization of abnormal echocardiography findings is 6±3 months.

Conclusion: Coronary artery involvement is seen in most of children with Kawasaki disease. Intravenous gamma globulin and aspirin has been reported to reduce the likelihood of development of giant coronary artery aneurysms and appears to have a direct beneficial effect on abnormalities in cardiac function associated with the acute phase of Kawasaki disease.

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Introduction:

Kawasaki disease (KD) is an acute febrile illness and systemic vasculitis of unknown etiology that predominantly affects infants and young children in small and medium sized vessels particularly the coronary arteries. The pathogenesis of Kawasaki Disease remains unclear. Several studies were conducted to determine the theory behind the development of Kawasaki disease based on genetic, immunologic, and infectious factors. Several studies found several associations between genetic and immunologic components in an attempt to identify the pathogenesis of coronary artery involvement in Kawasaki disease. The

most serious complication of KD is a coronary artery lesion including myocardial infarction, and coronary artery aneurysm (CAA).⁵ Coronary artery aneurysms as a sequela of vasculitis of KD occur in 20-25% of untreated children. In developing countries, KD has replaced acute rheumatic fever as the leading cause of acquired heart disease in children.⁶ Echocardiography plays an important role in identifying cardiac complications in KD.

The Japanese Ministry of Health Criteria first proposed the initial echocardiographic criteria in 2004, which was modified in 2008, which classified

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aneurysms as small aneurysms (Z score>2.5 to <5), medium aneurysms (Z score >5 to <10), and large aneurysms (Z score >10 to or more than 8 mm diameter).6 In 2017 the American Heart Association classified aneurysms with the help of Z scores. 7 Commonly used definitions of coronary artery involvement relied on the Japanese Ministry of Health criteria, which dichotomously define abnormalities as a maximum absolute internal diameter > 3 mm in children < 5 years of age or >4 mm in children 5 years and older ,or a segment 1.5 times greater than an adjacent segment, or the presence of luminal irregularity.⁸ A high prevalence of CAAs has been recently reported even among KD infants aged younger than six months. 9,10 Aspirin and intravenous immunoglobulins are two drugs conventionally used to treat Kawasaki disease. The initial treatment for Kawasaki disease combines amino salicylic acid (ASA) with intravenous immunoglobulins. 11 The most important part of treatment in Kawasaki disease is early detection and prevention of cardiac complications, especially coronary artery aneurysms. The present study was designed to analyze data from 149 children with Kawasaki disease from echocardiography laboratory of Lab Aid Cardiac hospital for coronary artery involvement, treatment protocols and outcome.

Methods:

This retrospective study included 149 patients with KD, diagnosed and treated between 1st January 2021 and 31 August 2022 at Lab Aid Cardiac Hospital, Dhaka. Patients were referred from other regional hospitals and pediatricians. Verbal/ written informed consent was obtained from all the parents. The data was collected from the database of echocardiography and outpatient department. Inclusion criteria for enrollment in the trial included- a) diagnosis of KD by meeting modified criteria from recent American Heart Association guidelines, 11 b) presentation within 10 days of onset of illness. Exclusion criteria for trial enrollment included prior treatment with intravenous immunoglobulin (IVIG) or steroids, and the presence of another disease known to mimic KD. Acquired or congenital heart disease and other chronic systemic disorders were excluded.

The diagnosis of KD was based on standardized assessments such as medical history, physical examination, and laboratory measurements. All baseline laboratory values were collected before treatment and included white blood cell count, hematocrit, platelet count, C-reactive protein, erythrocyte sedimentation rate, serum albumin, alanine amino transferase and urine leukocyte count. The abnormal values of lab results were recorded.

Patients were considered to have coronary artery abnormalities due to Kawasaki disease if either any coronary artery segment had a Z-score of >2.5, adjusted for body surface area, or if they met the Japanese Ministry of Health criteria for coronary artery abnormality. Z score were derived for the left main, right proximal, left anterior descending and circumflex arteries using equations from the echocardiography z score database. 16 In the present study, coronary artery involvement was associated with a high erythrocyte sedimentation rate, high platelet count, and low hematocrit and serum albumin level. These biomarkers were used to predict coronary artery involvement. All patients received a single dose IVIG along with aspirin. For patients with persistent or recurrent fever (fever after 3rd days of IVIG therapy) an additional dose of IVIG was given. Those patients who had Z score of more than 5 were treated with Warfarin and two cases with acute coronary syndrome (High cardiac troponin) were treated with Heparin infusion for 48 hours. Patients had standardized echocardiograms performed within 48 hours of enrollment (initial) and at 1 and 6 weeks after initiation of treatment.

Results:

Fourteen percent (table-I) cases were in age group 0 to 1 year, 54% aged 1 to 5 years, 31 % aged 5 years to 13 years. The median age of the study population was 36 months. Males outnumbered females in this study (1.8:1). During the survey period 149 patients (n=149) were diagnosed with KD at Lab aid cardiac hospital, based on the clinical findings that met the inclusion criteria. Most of the patients were transferred from pediatricians or other hospitals with a suspicion of Kawasaki disease.

Table-I Demographic profiles of the study population (N=149).

Gender	
Male	97 (65%)
Female	52 (35%)
Age	
0-<1 years	21 (14%)
1-5 years	81 (54%)
≥ 5 -13 years	47 (31%)

Table II

Frequency of hematological, biochemical markers and echocardiographic findings during 1^{st} evaluation (N=149).

Parameters	Number of	Percentage	
	patients		
High ESR	140	93.96	
Raised CRP	145	97.32	
Raised Platelet	142	95.30	
Raised Troponin-I	15	10.07	
Raised WBC	148	99.33	
Dilated Coronaries in	132	88.60	
echocardiography			
(Single & Multiple)			

Table-II Showing that Out of 149 cases 132 (88.60%) patients had coronary involvement, among them most of the patients experienced tubular dilatation of the coronary arteries and few had aneurysmal dilatation. The patients with dilatation of the coronary arteries had fever lasting more than five days, out of 149 cases, 140 (93.96%) patients had raised erythrocyte sedimentation rate (ESR) and showed a mean value of 80 mm/h. Most of the cases had leukocytosis (99.33%), higher CRP (97.32%) and thrombocytosis (95.30%) while they were hospitalized.

Treatment was given to all 149 patients (table-IV) with the administration of single infusion intravenous immunoglobulin 2 gm/kg over 12 hours at diagnosis of the disease along with high-dose aspirin. High dose aspirin (80-100mg/kg) in 4 divided-doses was continued during the initial phase of the disease until the patient was afebrile for 48 to 72 hours. This high dose of aspirin (80-100mg/kg) was followed by a low dose of aspirin (3-5 mg/kg) daily for 4-6 weeks or until no coronary artery abnormalities had been detected by echocardiography. Only 4 patients needed 2nd dose of high-dose IVIG. This standard treatment regimen for Kawasaki disease benefits in preventing coronary artery aneurysm development.

Table III

Frequency of coronary artery involvement at first evaluation (Dominant involvement) (N=132).

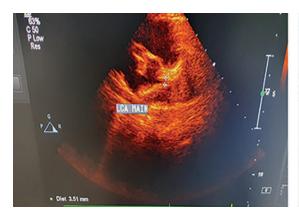
Z- ScoreCoronary artery	Dilated but	2.0 to	2.5 to	>5.0 SD	Total
	<2 SD	< 2.5 SD	<5 SD		N=132
Dilated MLCA	2 (4.1%)	13 (27%)	31 (64%)	2 (4.1%)	48 (36.37 %)
Dilated LAD	3 (8.1%)	10 (27%)	11 (29%)	13 (35%)	37 (28.03%)
Dilated LCX	0	7 (46%)	6 (40%)	2 (13%)	15 (11.37%)
Dilated RCA	5 (15.6%)	8 (25%)	8 (25%)	11 (34%)	32 (24.25%)
Multiple coronary dilation	09 (06.82%)	16 (12.13%)	35 (26.52)	20 (15.16)	80 (60.61%)

Table-III shows The number of cases with Z scores, Z scores were more than 2.5 SD mostly involving MLCA, and LAD and RCA.

Table-IV
Treatments given to patients with confirmed clinical criteria (N=149).

Treatment Given	Number of patients	Percentage
High Dose IVIG 2gm/kg(1st Dose)	149	100%
High Dose IVIG 2gm/kg(2 nd Dose)	04	3.03%
High Dose Aspirin80-100 mg/kg	149	100%
Low Dose Aspirin3-5mg/kg after acute phase	149	100%
Heparin infusion for 48 hours	2	1.34%
Warfarin	28	18.79%

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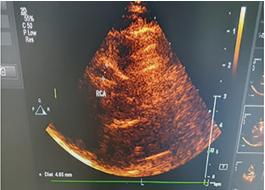


Fig.-1: Dilated coronary arteries in a case in first evaluation.

Table-V
Follow up evaluation of coronary arteries (N=149).

Coronaries	Within 48 hours	After one week	After six weeks
Dilated LCA	48 (36%)	74 (56.06%)	4 (3.0%)
Dilated LAD	37 (28%)	55 (41.67%)	5 (3.3%)
Dilated LCX	15 (11%)	18 (13.64%)	00
Dilated RCA	32 (24%)	39 (29.55%)	5 (3.3%)

Table-VIFrequency of coronary involvement after 6 weeks (N= 132).

	Dilated but <2 SD	2.0 to <2.5 SD	2.5 to <5.0 SD	>5.0 SD
Dilated M LCA	02 (4.55%)	02 (1.52%)	00 (00%)	00 (00%)
Dilated LAD	03 (2.28%)	02 (1.52%)	00 (00%)	00 (00%)
Dilated LCX	00 (00%)	00 (00%)	00 (00%)	00 (00%)
Dilated RCA	01 (0.76)	04 (03.03%)	00 (00%)	00 (00%)

Table V Shows initially LCA 48% and LAD 37% are mostly involved which has raised to LCA 74% and LAD 55% after a week but dramatically reduced at the 6th week of follow-up evaluation. Coronary artery involvement may not be present in first evaluation so treatment can prevent

development of such changes. Most of the affected coronary segments returned to normal after IVIG and high dose Aspirin over six weeks.

Table VI Shows significant reduction of coronary diameters after six weeks.





Fig-2: Normal coronary arteries after three months of diagnosis.

Discussion

The diagnosis of Kawasaki disease is made when five of the following six symptoms are present. Persistent fever lasting more than five days along with bilateral conjunctival congestion, mucosal involvement, non-suppurative cervical lymphadenopathy and polymorphous eruption and peripheral extremities involvement¹⁷. In 2004, The American Heart Association proposed its guidelines which include fever for five days with any four of the five clinical features (erythema of palms and sole, diffuse polymorphic eruptions, bilateral nonexudative conjunctivitis, mucosal involvement, cervical lymphadenopathy).¹⁸ Coronary artery aneurysms (CAA) are one of the triggers for the acute coronary syndrome as a complication of Kawasaki disease. KD is commonly diagnosed and reported in global populations, especially in Asia. 19 We have observed that the incidence of KD has increased in recent years in Bangladesh. With regard to age, KD generally occurs in children <5 years old.²⁰ Furthermore, with regard to gender, our study and others study showed that KD occurs more commonly in the male gender. 21 In this study, the mean age of KD patients was 36 months, while 68% of these individuals were under 5 years old. Similarly,73% and 85% of KD patients in Denmark and China were under the age of five, respectively.^{22,23}

In the present study in all patients with coronary artery involvement had significantly higher erythrocyte sedimentation rate, higher platelet counts and C reactive protein level. Cardiac troponin is a sensitive marker that was elevated in most of the children with KD during the acute phase. Ato et al. have measured cardiac troponin by a highly sensitive assay and showed that cardiac troponin levels are elevated in 15 of children with KD during the acute phase in his study. These levels may continue to remain elevated during the convalescent phase as well. ²⁴

This study observed that KD in children under five years of age were at a high risk of developing CAAs. Cardiac complications (especially CAAs) in 20% of Iranian children with KD were earlier observed. ^{25,26} 2D echocardiography remains the mainstay of imaging for cardiovascular assessment in KD both during acute phase and in

long term follow up.²⁷ In our study, three patients had an isolated aneurysm that was 4 mm in the right coronary artery. No patient had giant aneurysm. Abnormal vessel tapering was not assessed. If the maximum Z scores of the RCA and LAD were >5 at the initial echocardiogram, they did not increase >5 SD for 95% of such patients at subsequent echocardiograms after treatment. If the maximum z score was >5 at the initial echocardiogram, reduction to >2.5 over the 6 weeks' follow-up was observed in 80% of subjects. Linear regression analysis of repeated measures of z scores of the RCA and LAD occurred from the initial assessment to 6 weeks of follow-up. The administration of intravenous immunoglobulins within 10 days of onset of the illness can reduce the risk of the development of coronary artery aneurysms. 28 This high dose of aspirin is followed by a low dose of aspirin for its antiplatelet action and to prevent cardiac complications.²⁹

Another important consideration in the treatment of Kawasaki disease in the prevention of cardiac complications. In 2017 the American Heart Association (AHA) proposed effective follow-up strategies for early detection and prevention of cardiac complications of Kawasaki disease Pharmacological interventions such as lipidlowering drugs and anti-platelets like aspirin or clopidogrel should be advised.³⁰ Children treated with the single infusion regimen had significantly fewer coronary arterial abnormalities 2 weeks after enrollment. By the sixth week after enrollment, a single infusion regimen along with high-dose aspirin also had rapid regression and return to normal coronary arteries. A multicenter randomized controlled trial in the United States demonstrated that defervescence and resolution of inflammation were more pronounced and coronary arterial abnormalities were significantly less frequent in patients treated with intravenous gamma globulin plus aspirin.³¹ Children treated with the single infusion regimen also had a more rapid defervescence and return of acute phase reactants to normal.³²

In this study, most of the coronary artery changes returned to normal at 3rd evaluation at 6 weeks which corelates with another study conducted in Bangladesh.³³ Kawasaki disease is the commonest cause of myocardial infarction in children.³⁴ In two

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of our cases with Z score >5 and diameter more than 8 mm associated with high cardiac troponin were treated with heparin infusion for 48 hours.

Conclusion:

Coronary artery involvement is seen in most of children with Kawasaki disease. Intravenous gamma globulin and aspirin has been reported to reduce the likelihood of development of giant coronary artery aneurysms and appears to have a direct beneficial effect on abnormalities in cardiac function associated with the acute phase of Kawasaki disease.

Limitations of the study

This study is limited by its retrospective nature and relatively small sample size. By retrospective design, it was not possible to record laboratory results on a uniform day of illness. We, therefore, utilized the most abnormal laboratory result along with clinical features prior to IVIG administration which has the potential to lead to bias due to extreme value.

Conflict of Interest - None.

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