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Original Research Article

Comparison of clinico-haematological and echocardiographic features at diagnosis between complete and incomplete Kawasaki disease: a 12-years single centered experience from a tertiary care referral center of Bangladesh

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ABSTRACT

Background: Kawasaki disease (KD) is the most common cause of acquired heart disease in childhood with coronary artery abnormalities among 15-25% of cases. This study aimed to compare the clinico-haematological profile and initial echocardiographic changes of coronary arteries among complete and incomplete KD patients admitted in a tertiary care center in Bangladesh.
Methods: This was a retrospective study of 66 children diagnosed with KD admitted in the Department of Paediatrics from July 2010 to March 2023 at Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh.
Results: In our study, 51.5% patients had complete KD while 48.5% had incomplete KD. Children with incomplete KD (9.23±4.74 days) had a longer-lasting fever in comparison to complete KD patients (7.36±3.21 days). All the typical clinical symptoms of KD were observed significantly less frequently in children with incomplete KD. Laboratory findings between the two groups showed no significant differences. We observed that children with incomplete KD had significantly higher frequency of abnormal coronary artery at diagnosis (67.7%) in comparison to children with complete KD (34.3%). Here, children with incomplete KD had significantly higher frequency of at least one coronary artery aneurysm and mild coronary artery aneurysms in relation to complete KD patients.
Conclusions: All the typical clinical symptoms of KD were observed significantly less frequently along with longer dutration of fever in children with incomplete KD. Laboratory findings between the two groups showed no significant differences. Children with incomplete KD had significantly higher frequency of abnormal coronary artery at diagnosis in comparison to complete KD patients.

Keywords: Complete KD, Coronary artery aneurysm, Kawasaki disease, Incomplete KD

INTRODUCTION

Kawasaki disease (KD) is one of the most common forms of vasculitis in children under five years of age. The exact cause of this disease remains unknown.[1] It was first described by Dr. Tomisaku Kawasaki in 1967.[2] The incidence of KD has been increasing steadily.[3] It occurs 10 to 30 times more frequently in Northeast Asian countries, including Japan, South Korea, China, and Taiwan, compared to the United States and European countries. In 2014, 308 children under five were diagnosed with KD in Japan. In contrast, the incidence of KD in the United States was reported to be 19.1 cases per 100,000 children under five years old in 2015.[4] Additionally, the incidence rate of KD in Chandigarh, North India, was 4.7 cases per 100,000 children in 2009

and decreased to 1.11 cases per 100,000 in 2012.[5] KD is diagnosed clinically based on the criteria outlined in the 2017 AHA guidelines.[6] Children who have a fever lasting for five or more days, along with four or more of the five major clinical features namely conjunctival injection, cervical lymphadenopathy, oral mucosal changes, a polymorphous rash, and swelling or redness of the extremities are classified as having complete KD. Those who have a fever for five days or more and exhibit at least two of the major features that cannot be explained by other diseases are diagnosed with incomplete KD.[6] KD has the potential to impact both small and medium-sized blood vessels. Timely treatment is crucial, as coronary artery abnormalities can arise in 15-25% of children with KD when care is delayed or not administered.[6,7] This highlights the importance of prompt medical intervention, as KD has emerged as the leading cause of acquired heart disease in children due to its particularly strong effects on the coronary arteries.[8,9] In the acute phase of KD, which typically lasts from the initial 10 to 14 days of illness, conditions such as myocarditis and pericarditis are frequently observed.[10] Meanwhile, coronary artery aneurysms usually present 2 to 4 weeks after the onset of the illness. Early diagnosis of these aneurysms is essential, and imaging techniques like echocardiography play a vital role in this process.[11] Research indicates that children under 12 months and those over 10 years old are at a higher risk for developing coronary artery abnormalities, making it essential for healthcare providers to monitor these age groups closely.[12,13] The risk of coronary artery complications is significantly heightened by factors such as prolonged fever, low hemoglobin levels according to age and sex, an elevated neutrophil-to-lymphocyte ratio, and initial thrombocytopenia.[14-16] Administration of intravenous immunoglobulin (IVIG) within the first 10 days of illness is highly effective in reducing the risk of cardiac complications.[17-19] This reinforces the need for prompt treatment, as delaying IVIG beyond 10 days can more than double the risk of developing coronary artery aneurysms.[20]

Some patients may not meet all the criteria for Kawasaki Disease (KD) but are still at risk for developing coronary artery disease. These incomplete forms of KD are increasingly recognized, although a clear definition has yet to be established. Diagnosing incomplete KD can be challenging, and making therapeutic decisions is complicated.[21] Previous studies have indicated that incomplete KD is associated with delayed diagnosis and treatment, and that such delays can increase the risk of developing coronary artery lesions (CALs).[22] To prevent the development of CALs in patients with KD, it is crucial to identify and manage the risk factors associated with incomplete KD.[22] This study aims to compare the clinical profiles, laboratory results, and echocardiographic changes of coronary arteries in patients with complete versus incomplete KD.

METHODS

A total of 66 children below the age of 18 years clinically diagnosed as Kawasaki disease (KD) according to diagnostic criteria of American Heart Association (AHA) guidelines[6] admitted at in-patient department of Paediatric Rheumatology Division, Department of Paediatrics, BSMMU during the study period were enrolled as cases in this study. Children with fever for ≥5 days along with ≥4 of the major features like conjunctival injection, cervical lymphadenopathy, oral mucosal changes, polymorphous eruption and swelling or redness of the extremities were diagnosed as complete KD. But patients with ≥5 days fever and at least 2 major features that can't be explained by other diseases were enrolled as patient with incomplete KD in this study. Meanwhile, KD patients with evidence of infection, other vasculitis, inflammatory disease or known cases of cardiac disease were excluded from the study.

The study was performed by the ethical standards stated in the 1964 Declaration of Helsinki and its later amendments. Because of the study's retrospective nature, obtaining written informed consent from the patients was not required. The study protocol was reviewed and approved by the ethical committee of BSMMU. All the relevant data were collected from the electronic database and written records of patient's profile of Paediatric Rheumatology division, Department of Paediatrics, BSMMU. A data collection sheet was developed containing demographic information, initial clinical presentation, hematological parameters, and echocardiographic findings. Demographic variables included total number of cases, gender, mean age and distribution of disease onset among different age categories and seasonal variation. Clinical variables comprised of duration of fever, maculopapular rash, oral mucosal changes, conjunctivitis, cervical lymphadenopathy, extremity changes like edema, peeling, other systemic involvements, complications and type of KD (complete or incomplete KD). Relevant laboratory findings included complete blood count with ESR, CRP, ALT, urine RE were recorded also in data collection sheet. Echocardiography was performed by GE Echo machine Model Vivid E95 at the Department of Paediatric Cardiology, BSMMU. Patients were examined in supine and lateral position. All standard echocardiographic views: apical 4 chamber and 5 chamber, parasternal long axis, short axis, ductal, suprasternal and subcostal views were recorded in all patients and 4MHZ(4s), 5MHZ(5s) and 6MHz(6s) probes were used. Left coronary artery (LCA), left circumflex artery (LCX) and right coronary artery (RCA) diameters were measured and Z score was calculated using age, sex, weight, height and body surface area of the patients. According to AHA guideline 2017 Z-Score classification of coronary artery is as follows: No involvement: always <2, dilation only: 2 to <2.5, small aneurysm: ≥2.5 to <5, medium aneurysm: ≥5 to <10 or an absolute dimension of >4 mm to <8 mm and large or giant aneurysm: ≥10 or an

absolute dimension of ≥8 mm.[6] Appropriate statistical test were used to analyze the data of demographic, clinical, laboratory and echocardiographic findings. Non-normally distributed quantitative variables were expressed by median with interquartile range and frequency distribution were calculated by percentages. Statistical analysis to compare between two categorical variables were done by using chi-square test and between two quantitative variables were done by using independent samples t-test. P values less than 0.05 were considered statistically significant.

RESULTS

A total of 66 patients diagnosed and admitted as KD at in-patient department of Paediatric Rheumatology Division, Department of Paediatrics, BSMMU were considered as case in this retrospective study. We found that 34 (51.5%) patients had complete KD while the remainder 32 (48.5%) patients were diagnosed as incomplete KD in this study. Table 1 showed that the mean age of complete KD and incomplete KD were 4.54 years and 5.34 years respectively. There was no statistically significant difference between the two groups regarding mean age. We also observed male predominance in both complete KD (82.4%) and incomplete KD (65.6%) without any statistically significant difference between this two groups.

Table 1: Comparison of demographics features between complete and incomplete KD patients.

Patient's characteristics		Complete KD (n=34) (%)	Incomplete KD (n=32) (%)	P value
Age in years, (mean±SD)		4.54±2.75	5.34±2.76	0.241
Age (years)	0-5	22 (64.7)	16 (50)	0.472
	6-10	11 (32.4)	15 (46.9)	
	>10	1 (2.9)	1 (3.1)	
Gender	Male	28 (82.4)	21 (65.6)	0.12
	Female	6 (17.6)	11 (34.4)	

In our study, we found that children with incomplete KD (9.23±4.74 days) had a longer-lasting fever in comparison to complete KD patients (7.36±3.21 days) which was statistically significant. All the typical clinical symptoms of KD were observed significantly less frequently in children with incomplete KD with skin rash being the most common symptom in both groups (Table 2).

Table 3 demonstrated comparison of laboratory investigation findings between the two groups which revealed no statistically significant differences in laboratory parameters like haemoglobin, total white cell count, platelet count, C-reactive proteins (CRP), erythrocyte sedimentation rate (ESR), haemoglobin and alanine aminotransferase (ALT).

Table 2: Comparison of clinical features between complete and incomplete KD patients.

Clinical features	Complete KD (n=34) (%)	Incomplete KD (n=32) (%)	P value
Fever duration (days) (Mean±SD)	7.36±3.21	9.23±4.74	<0.001
Maculopapular rash	29 (85.3)	18 (56.3)	0.009
Cervical lymph node	22 (64.7)	11 (34.4)	0.014
Oral mucosal changes	26 (76.5)	12 (37.5)	0.011
Conjunctivitis	23 (67.6)	9 (28.1)	0.001
Extremity changes	26 (76.5)	15 (46.9)	0.013

Table 3: Comparison of laboratory findings between complete and incomplete KD patients.

Investigations	Complete KD (n=34)	Incomplete KD (n=32)	P value
Haemoglobin (g/dl)	10.74±1.49	10.79±1.27	0.865
White blood cell count (cells/mm^3)	14113.82±6513.66	14254.37±5929.21	0.927
Platelet count (cells/mm^3)	495029.41±234888.56	429000.00±177095.19	0.204
ESR (mm in 1st hour)	48.41±30.03	59.69±30.55	0.063
CRP (mg/L)	68.24±48.47	51.46±63.83	0.232
Serum ALT (U/L)	50.47±74.12	42.52±36.49	0.586

Table 4: Comparison of coronary artery involvement at diagnosis between complete and incomplete KD.

At diagnosis	Complete KD (n=34) (%)	Incomplete KD (n=32) (%)	P value
No coronary artery involvement	23 (67.7)	11 (34.3)	0.007
Abnormal coronary artery	11 (32.3)	21 (65.7)	0.007
At least one coronary artery dilatation only	2 (5.9)	3 (9.4)	0.592
At least one coronary artery aneurysm	9 (26.4)	18 (56.3)	0.014
Small aneurysm	5 (14.7)	12 (37.5)	0.034

Continued.

At diagnosis	Complete KD (n=34) (%)	Incomplete KD (n=32) (%)	P value
Medium aneurysm	3 (8.8)	4 (12.5)	0.628
Large aneurysm	1 (2.9)	2 (6.3)	0.519

In this current study, we observed that children with incomplete KD had significantly higher frequency of abnormal coronary artery at diagnosis (67.7%) in comparison to children with complete KD (34.3%). We also demonstrated that children with incomplete KD had statistically significant higher frequency of at least one coronary artery aneurysm and mild coronary artery aneurysm events in relation to complete KD patients (Table 4).

DISCUSSION

In this study, we observed the mean age of complete KD and incomplete KD were 4.54 years and 5.34 years respectively. There were no statistically significant difference between the two groups regarding mean age. We also found no significant differences in different age categories between the 2 groups. A study conducted by Kolko et al, 2023 also showed similar findings with no significant difference between complete and incomplete KD patients in respect to mean age of the patients.[23] Our study showed male predominance in both complete and incomplete KD groups without any statistical difference between this two groups. A north Indian study also demonstrated parallel findings to our study which showed male predominance with no significant differences between the 2 groups.[24] This study demonstrated a slightly more prevalent of complete KD cases (51.5%) in comparison to incomplete KD cases (48.5%). Corresponding results were observed in a study conducted at Saudi Arabia showed the number of cases in both groups were equal.[23] Another study by Banoo et al. 2021 showed distinctly higher predominance of complete KD cases (61.3%) than incomplete KD cases (38.7%).[24] These variations in demographic variables may be due to geographical location, ethnicity and genetic variability.

In our study, we observed that children with an incomplete KD had a longer-lasting fever. The typical clinical symptoms of KD were significantly less frequent in children with incomplete KD with skin rash being the most common symptom in both groups. A surveillance study done in Switzerland also demonstrated almost similar findings regarding comparison of clinical features among complete and incomplete KD groups.[25] These differences can be explained by more comprehensive presentation of clinical features required to meet the diagnostic criteria of complete KD in comparison to incomplete KD.

In this current study, comparison between the two groups revealed no statistically significant differences in laboratory parameters like haemoglobin, total white cell count, platelet count, C-reactive proteins (CRP), erythrocyte sedimentation rate (ESR), haemoglobin and alanine aminotransferase (ALT). Similar findings were demonstrated at a north Indian study by Banoo et al and at Saudi Arabia by Kolko et al regarding laboratory findings among complete and and incomplete KD patients.[23,24] These findings may be explained as complete and incomplete presentations are two ends of the same disease spectrum and do not represent two different disease entities. Incomplete KD children do not present with atypical features; rather they simply do not present with the full clinical spectrum typical of the disease.[26]

In our study, we observed that children with incomplete KD had significantly higher frequency of abnormal coronary artery at diagnosis 67.7% in comparison to children with complete KD 34.3%. We also demonstrated that children with incomplete KD had significantly increased frequency of at least one coronary artery aneurysm and mild coronary artery aneurysm in relation to complete KD. A North Indian study also showed similar findings to our study where coronary artery abnormalities were 36.8% in the complete KD group and 83.3% were in the incomplete KD group and the difference was statistically significant.[24] There are several other published studies which have shown that incomplete KD is associated with a higher risk of developing coronary abnormalities.[22,27] The higher prevalence of coronary artery lesions in incomplete KD reflects a diagnostic bias because of the use of echocardiography and difficulties in making the diagnosis leading to treatment delay.[22] More intensive treatments of patients with incomplete presentations, possibly to the same level that is performed in complete KD patients, could lead to the further reduction of coronary artery lesions.[22]

Our study has some limitations. Firstly, there is no standardized method for diagnosing incomplete KD in cases without coronary artery abnormalities (CAA). While the diagnostic algorithm from the AHA in 2004 is useful, it does not fully eliminate the risk of misdiagnosis. A comprehensive understanding of KD's pathogenesis and the identification of pathogenic markers may enhance diagnostic accuracy. Secondly, the studies analyzed were non-randomized, retrospective case–control studies conducted over a 12-year period. This duration has seen variations in disease recognition, treatment approaches, and diagnostic protocols for incomplete KD, resulting in significant variability that may limit the reliability of findings. Additionally, there is potential for sampling errors and publication bias. Given these limitations, the results of our study should be interpreted with caution. Future prospective cohort

studies may help address these issues and provide clearer insights beyond those inherent in this retrospective study.

CONCLUSION

Children with incomplete KD had longer duration of fever in comparison to complete KD patients. All the typical clinical symptoms of KD were observed significantly less frequently in children with incomplete KD with skin rash being the most common symptom in both groups. Laboratory investigation findings between the two groups showed no significant differences. Children with incomplete KD had significantly higher frequency of abnormal coronary artery at diagnosis in comparison to children with complete KD.

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