

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF KAWASAKI DISEASE WITH SPECIAL REFERENCE TO CARDIAC INVOLVEMENT*Jayanta Kumar Poddar¹, Soma Saha², Jayanta Debnath³*

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ABSTRACT**BACKGROUND**

Kawasaki disease (KD) is an acute medium vessel vasculitis with multisystem involvement especially in young children of unknown etiology and present as acute febrile illness. It is the leading cause of acquired heart disease in children across the globe.

OBJECTIVES

We aimed to evaluate the epidemiological characteristics, clinical manifestations and cardiac involvement of KD in children residing in Tripura, a North Eastern State of India.

MATERIALS AND METHODS

In this retrospective study, we reviewed the medical records of all children with KD who had been admitted in Pediatric ward of Tripura Medical College & DR BRAM Teaching Hospital, Agartala from March 2007 to February 2015. Data regarding clinical, epidemiological characteristics, Cardiac involvement, laboratory parameter, management, and the outcome of disease for each patient were obtained. The patients were divided into cardiac and non-cardiac groups based on echocardiographic results.

RESULTS

In total, 30 patients with KD (18boys and 12 girls) were enrolled in this study. The male to female ratio was 1.5:1. The median age at diagnosis was 15 months, and the diagnosis was made after a mean of 8.1 days of fever. A seasonal peak during the winter-spring months was observed. 23 (76.6%) had classical presentation of KD. Fever, polymorphs, skin rash, conjunctivitis, changes in the oropharynx were the most common manifestations. Cardiac involvement was detected in 7(23.3%)%, with coronary artery abnormalities (CAA) and 26(86.5%) patient showed ECG abnormality. Patients were treated with immunoglobulin and aspirin. The CAA regressed in all patients but one persisted even after 12 months.

CONCLUSION

Kawasaki disease is not rare in Tripura. The age, gender distribution and clinical findings are similar to that of other reports. Patients with cardiac abnormalities had delayed treatment and prolonged hospital stays.

KEYWORDS

Kawasaki Disease, Epidemiology, vasculitis, echocardiography, Tripura.

HOW TO CITE THIS ARTICLE: Poddar JK, Saha S, Debnath J. Clinical and epidemiological characteristics of kawasaki disease with special reference to cardiac involvement. J Evid Based Med Healthc 2016; 3(1), 1-5.

DOI: 10.18410/jebmh/2016/1

INTRODUCTION: Kawasaki Disease (KD) is an acute medium vessel vasculitis with multisystem involvement especially in young children of unknown aetiology and present as acute febrile illness.^[1]

Submission 22-12-2015, Peer Review 23-12-2015,

Acceptance 29-12-2015, Published 02-01-2016.

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DOI: 10.18410/jebmh/2016/1

KD was first reported by a Japanese paediatrician, Tomisaku Kawasaki, in 1967 in a Japanese language journal, *Arerugi*.^[2] He described 50 children who appeared to have a unique set of clinical features which he called the 'Mucocutaneous lymph node syndrome'.^[1] This was initially thought to be a benign clinical condition but soon it was realized that some children went on to develop coronary artery aneurysms. KD has now been described from all over the world.^[3]

The aetiology of KD is still unknown and no single pathognomonic clinical or laboratory findings for its definitive diagnosis have been identified.^[4] The diagnosis of KD was based on the diagnostic guidelines reported by the American

Heart Association Committee on Rheumatic Fever, Endocarditis, and KD.^[5] Diagnosis of classical KD is based on clinical criteria which includes:

1. Fever of at least five days duration.
2. Presence of any four of the following five features:
 - (a) Changes in extremities,
 - (b) Polymorphous exanthema,
 - (c) Bilateral non purulent conjunctivitis,
 - (d) Changes in the lips and oral cavity and
 - (e) Cervical lymphadenopathy.
3. Exclusion of other diseases with similar findings.

Children presenting less symptoms than the four classical features of KD are said to have "incomplete or atypical KD".^[4] Incomplete KD is more common in young infants than in older children, and leads to inaccurate diagnosis and timely treatment and who are at risk of developing coronary abnormalities, thus confirming the diagnosis of KD as a systemic vasculitis syndrome having heterogeneous features rather than a single clinical entity.

Fever is typically hectic and remittent, with peak temperatures frequently exceeding 39°C or higher. The fever is unresponsive to antibiotics but partially responds to antipyretics. For untreated children, the febrile period lasts for a mean of 11 days.^[1]

Bilateral painless vascular injection of the bulbar conjunctivae is generally seen in the first week of illness. Patients sometimes have follicular palpebral conjunctivitis. Conjunctival injection is not associated with exudate, oedema or corneal ulceration.

Cervical lymphadenopathy (LA) is usually variable and seen in 50-70% of patients. LA is unilateral and confined to the anterior cervical triangle. The enlarged node or mass of nodes is usually more than 1.5 cm, is non-fluctuant, may or may not be associated with erythema of the overlying skin and is only moderately tender.^[1]

Changes in the mouth and lips are characterized by erythema, dryness, fissuring, cracking and bleeding of the lips, diffuse erythema of the oral and pharyngeal mucosa, strawberry tongue with erythema and prominent papillae. Oral ulceration, exudates, and Koplik's spots rarely, if ever, are found in KD.^[6]

Rashes in KD tend to be most prominent on the trunk but frequently also involve the face and extremities.^[1] Rashes in KD may take any of the several forms. The most common is macular-papular, primarily truncal erythematous rash. A scarlatiniform rash and an erythema multiforme like rash with target lesions are also seen. Perianal rashes have been emphasized by many observers.^[1]

Changes in the hands and feet include redness of the palms and soles often accompanied by a characteristic 'indurative oedema' on the dorsal aspects. This is almost pathognomonic of KD. These changes are, however, only seen in the acute phase and may have completely disappeared by the end of the second week. These peripheral changes are followed by a typical periungual desquamation of fingers and toes in the subacute stage of the illness. One to two months after the onset of KD, transverse ridged

grooves may develop across the base of the nails (Beau's lines) and grow out with the nail. Beau's lines comprise the only clinical finding of KD that can be seen for several weeks.^[2]

The other associated features of KD include: extreme irritability that is especially prominent in infants, sterile pyuria, mild hepatitis, obstructive jaundice, arthralgia and arthritis, aseptic meningitis, diarrhoea, cardiomyopathy, pericardial effusion, myocardial infarction.^[1] Erythema, induration or crust at the BCG inoculation site are listed as significant findings among the diagnostic guidelines for KD by the American Heart Association.^[5]

There is no specific diagnostic test for KD, but there are certain laboratory findings are characteristics. This disease is characterized by leukocytosis, especially granulocytosis with high band form counts, and elevated platelet in the second and third weeks of the illness. Anaemia may develop, usually with normal red blood cell indexes. Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and other acute phase reactants are present in the acute phase of the disease. Moderate elevation in serum transaminases and hypoalbuminemia occur in these patients.^[1] Administration of high dose intravenous immunoglobulin (IVIG) in combination with aspirin treatment, within the first 10 days after the onset of fever, has been shown to reduce the rate of major complications (coronary artery abnormalities) from 20-25% to 3-5%.^[7,8]

Kawasaki disease is diagnosed after exclusion of other diseases, and the differentiation between KD and similar diseases is sometimes difficult. Better recognition of various presentations of KD helps prevent misdiagnosis and over-diagnosis of this disease. Considering that 20% of patients with KD develop coronary artery abnormalities and some of these patients do not fulfil the classic criteria for KD, better recognition of presenting signs and symptoms of KD is important for early diagnosis of the disease and prevention of complications.

To the best of our knowledge there have been no comprehensive studies on patients with KD in Tripura, we conducted a retrospective study of the epidemiological characteristics, clinical manifestations, and laboratory findings of KD in a Tertiary care Teaching Hospital of Tripura. The objective of this study was to determine the most common clinical, epidemiological features and cardiac abnormalities of KD in order to improve early diagnosis of this disease and prevent its complications.

MATERIAL AND METHODS: In this retrospective study, we reviewed the medical records of all children with KD who had been admitted to Paediatric ward of Tripura Medical college & DR. BRAM Teaching Hospital, Agartala from March 2007 to February 2015. All patients who met the criteria for KD, according to the American Heart Association and American Academy of Pediatrics guidelines, were included in the study.^[5] Information concerning epidemiological characteristics, clinical manifestations, laboratory, Electrocardiography (ECG) and echocardiographic findings, disease management and outcome for each case was

obtained. ECG was done in all cases irrespective of cardiac involvement on admission, discharge and on follow up. Echocardiography was performed upon diagnosis, and one week, three weeks, three months, six months and one year after diagnosis. Continuous variables (such as age) were expressed as the mean, median, and range. Absolute numbers as well as percentages are presented for the study variables. As this is a descriptive study and sample size is very small no statistical tests of significance were used.

RESULTS: In total, 30 patients were enrolled in our study. Amongst these cases 18(60%) were boys and 12(40%) girls (male to female ratio=1.5:1). The age of the patients ranged from 6 weeks to 8years. Most of the patients were from urban 23(76.6%) and 7(23.3%) patients from rural area. More patients were seen during winter (46.6%) and spring (33.3%), but this difference was not significant (P=0.33). Most patients were referred to the hospital during February and April.

As to ethnicity, 23(76.6%) patients were of Bengali Hindu origin, 5(16.6%) of tribal origin and 2(6.6%) Bengali Muslim origin. There were 18 males and 12 females, with a male to female ratio of 1.5:1. The mean age at diagnosis was 25.5 months and the median was 15 months (range 6 weeks to 8 years). Twelve (40%) children were diagnosed at less than one year of age, 16(53.3%) at less than 5 years of age and 2(6.6%) above 5years of age. The disease occurred during the winter season in 14 cases (46.6%), spring in 10 (33.3%), summer in 4(13.3%), and autumn in 2(6.6%) [Table 1]. The classical diagnostic criteria for KD were fulfilled in 23(76.7%) patients. Only 7(23.3%) cases were diagnosed with incomplete criteria (five patients with a positive echocardiogram and two after exclusion of other possible diagnoses).

The clinical findings essential for the diagnosis of KD together with the associated clinical and laboratory findings were used for the diagnosis of KD in all patients. The Frequency of KD criteria among the patients were observed as: fever was present in all of the patients 30(100%), Polymorphs and skin rashes 28(93.3%) each, conjunctivitis 27(90%), oral mucosal changes 27(90%), Extremities changes 21(70%) and cervical Lymphadenopathy 18(60%). The associated clinical features includes irritability, coryza, perineal erythema, arthralgia and vomiting. [Table 2]

Electrocardiogram (ECG) done in all 30 patients of KD. 26(86.5%) patient showed ECG abnormality. In our series raised S-T segment in 11(26.6%), prolong corrected QT interval(QTc) in 8(26.6%), increased Q/R ratio in 7(23.3%). [Table 3] Prolonged QTc persisted in one case even after one year follow up. Among the children in the current series, 7(23.3%) had cardiac involvement. Pericardial effusion occurred in 3(9.9%) cases. The effusion was minimal and transient in most of the cases. Coronary artery involvement was observed in 7(23.3%), of which 5(16.6%) had Aneurysm, small (<5mm) 3(9.9%), Medium (>5-<8mm) 2(6.6%). Cardiac Function was normal in 30(100%). [Table.4]

Laboratory findings of the children are summarized in [Table 5]. Most patients had high ESR 90% and WBC with predominance of neutrophils. Anaemia for age was detected in 76.6% Of cases. Leucocytosis in in 70% and thrombocytosis (either on presentation or towards the end of the second week of illness) in 86.6%. Elevated transaminases in 27%, low serum albumin in 80% and sterile pyuria in 30% cases.

Sl. No.	Demographic characteristic	Value	
1.	Age at presentation (6 weeks to 8 years)	Mean	25.5 months
		Median	15 months
2.	Gender [n (%)]	Male	18(60)
		Female	12 (40)
		Male: Female	1.5:1
3.	Ethnicity [n (%)]	Hindu Bengali	23(76.6)
		Tribal	5(16.6)
		Muslim Bengali	2 (6.6)
4.	Age distribution [n (%)]	≤1year	12(40)
		>1to ≤5years	16(53.3)
		>5years	2(6.6)
5.	Seasonal pattern [n (%)]	Winter	14(46.6)
		Spring	10(33.3)
		Summer	4 (13.3)
		Autumn	2 (6.6)

Table 1: Demographic and epidemiological data of patients with Kawasaki disease. [N=30]

Sl. No.	Signs and Symptoms	Results [n (%)]
01.	Fever	30(100)
02.	Skin rashes	28(93.3)
03.	Conjunctivitis	27(90)
04.	Oral changes	27(90)
05.	Extremities changes	21(70)
06.	Cervical lymphadenopathy	18(60)
07.	Irritability	15(50)
08.	Anorexia	10(33.3)
09.	Perianal erythema	8(26.6)
10.	Coryza	7(23.3)
11.	Cough	7(23.3)
12.	Vomiting	6(20)
13.	Arthralgia	6(20)
14.	Diarrhoea	2(6.6)
15.	Hepatomegaly	2(6.6)

Table 2: Clinical manifestations of children with Kawasaki disease (N=30)

Sl. No.	ECG abnormality	[N(%)]
01.	Prolonged corrected QT interval	8(26.6%)
02.	Raised S-T segment	11(36.6%)
03.	Increased Q/R ratio	7(23.3)
04.	Sinus Tachycardia	20(66.6)

Table 3: ECG abnormalities in Kawasaki disease

Sl. No.	Cardiac involvement	N (%)
01.	Total cardiac involvement	7(23.3)
02.	Coronary artery involvement	7(23.3)
03.	Aneurysm	5(16.6)
04.	Small (<5 mm)	3(10)
05.	Medium (>5-<8 mm)	2(6.6)
06.	Coronary artery dilation (ectasia)	1(3.3)
07.	Pericardial effusion	3(10)
08.	Mitral/tricuspid regurgitation	2(6.6)
09.	Normal bi ventricular function	30(100)

Table 4: Echocardiographic findings in patients with Kawasaki disease

Sl. No.	Investigation	Result [n (%)]
1.	Anaemia	23 (76.6%)
2.	Leukocytosis (WBC \geq 12 \times 10 ⁹ /L)	21(70%)
3.	Thrombocytosis (\geq 450 \times 10 ⁹ /L)	26(86.6%)
4.	Increased ESR	27(90%)
5.	Positive C-reactive protein	27(90%)
6.	Increased liver enzyme (ALT/AST)	9(27)
7.	Albumin (serum level \leq 3 gm/dl)	24(80%)
8.	Sterile pyuria (WBC \geq 5/HPF)	9(30%)

Table 5: Laboratory results of patients with Kawasaki disease (N=30)

WBC-White Blood Corpuscles; ESR-Erythrocyte Sedimentation Rate; ALT-Alanine Aminotransferase; AST-Aspartate Aminotransferase.

DISCUSSION: Kawasaki disease is a relatively common disease in India. [9,10] We reported the epidemiological characteristics, clinical manifestations, management, and disease outcome for children with KD in this North eastern State of India, Tripura. The mean age at the onset of the disease (25.5 months) was similar to the mean age reported from Iran, Jamaica, china, and Korea. [11] The male preponderance in this study was similar to most studies, yet lower than studies from China and Sweden. [9,12] In our study, similar to a study from the United States of America, the disease was more common in winter and spring yet, in other studies, KD had a peak incidence during other seasons. [13]

The clinical manifestations of KD in our study were similar to other studies. Skin rash, Oral changes and conjunctivitis were the most common cardinal features [9,14] while

lymphadenopathy was the least common cardinal sign. [11,15] The high rate of white blood cells (WBC), polymorphonuclear (PMN) leukocytes, platelet count and ESR was similar to other reports. [14,16] This study was a retrospective study and had the limitations of this type of studies.

In regards to the considerable number of patients with incomplete KD, for each young child with prolonged and unexplainable fever, KD should be considered during the differential diagnosis. In this study, 7(23.3%) patients had cardiac abnormalities that is similar like other Indian study. [10,17] The frequency of cardiac abnormalities are different in reports from Thailand (6.2%), Hong Kong (15%), USA (17%), Oman (25%), Finland (28%), China (32%), and Turkey (33%) Saudi Arabia (51%). There was no significant difference between the cardiac and non-cardiac patients except for the duration of hospital course and interval between onset of disease and treatment. A considerable portion of patients, do not fulfil the criteria of classic KD (incomplete KD). The rate of cardiac abnormality is 23.3% and patients respond well to administration of IVIG and aspirin. Prolonged fever and delayed treatment were risk factors for developing cardiac abnormalities. Similar to some studies, in patients with cardiac abnormalities, the treatment begun later and the hospital course was longer. [15] In one study from Pakistan, delayed treatment and fever more than 10 days at the time of initial presentation were risk factors for development of cardiac abnormalities. [15] Transient ECG changes were noted in most of the cases of KD irrespective of cardiac abnormalities detected by echocardiography. In the present study 26(86.5%) showed ECG abnormalities which is similar to a study reported from Singapore. [18] Isolated sinus tachycardia may be related to fever. It has been postulated that children with incomplete disease are at higher risk of developing CAA than those with classical presentations. [12] Thus, KD should be part of the differential diagnosis, particularly in younger children with fever and less than four criteria that have suggestive laboratory findings such as an increased white blood cell count (WBC), ESR, CRP, or thrombocytosis after 7 days of fever. [19] In this study, the mean duration of fever at diagnosis was 8.1 days. Seventy-eight percent of the cases had been diagnosed within 10 days after the onset of fever.

In this study, the response of patients to IVIG and aspirin was good and fever subsided shortly (24-48hrs) after IVIG administration. Cardiac abnormalities resolved in all patients except one. One limitation of our study was very small sample size and it is a retrospective study so some records were missing.

CONCLUSION: The finding of this study documents the incidence of Kawasaki disease in this region of the Indian and confirms the clinical similarities with various reports from other parts of the world. Early diagnosis and prompt treatment are crucial in preventing serious complications. A prospective study involving all state and district level Hospital is necessary to investigate the overall incidence and magnitude of Kawasaki disease in Tripura.

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