KAWASAKI DISEASE EXPERIENCE AT TERTIARY CARE HOSPITAL RAWALPINDI, PAKISTAN

Syed Awais Ul Hassan Shah, Shahid Mahmud*, Shahneela**

Combined Military Hospital Jhelum/National University of Medical Sciences (NUMS) Pakistan, *Pakistan Naval Ship Shifa Karachi Pakistan, **Central Ammunition Depot Kirana Sargodha Pakistan

ABSTRACT

Objective: To study the clinical features, investigations, cardiac complications, effects of treatment and demographic profiles in patients with classical Kawasaki disease (KD).
Study Design: Descriptive study.
Place and Duration of Study: Pak Emirates Military Hospital Rawalpindi, from Jan 2007 to Dec 2011.
Patients and Methods: Twenty five children of either gender aged 2 months to 12 years diagnosed with KD based on the international diagnostic criteria were included in this study. Collected data included patient demographics, clinical features, investigations, echo-cardio graphic findings, treatment and follow-up.
Results: A total of 25 patients were evaluated during the above mentioned duration. Mean age at diagnosis was 3.7 years (SD ± 3.05). Fever was present in 100% of the patients with the other major diagnostic features present in more than 90% of the patients. Seventeen (68%) patients presented after ten days of fever. Coronary aneurysms were seen in 40% of the patients. We administered intravenous immune-globulins (IVIG) in 100% of the patients. 12% of the patients still had coronary aneurysms after 1 year of diagnosis. There was no mortality.
Conclusion: KD needs to be considered in the differential diagnosis of all children with persistent unexplained fever with rash. A great number of cases of KD are missed and treated as common cold or flu. Diagnostic criteria used for KD is helpful in diagnosis of KD and can help in early prompt treatment with IVIG to prevent the life threatening complication of coronary aneurysms.

Keywords: Cornonary artery aneurysms, Diagnostic criteria, Echocardiography, Fever with rash, Kawasaki disease, Pakistan, Intravenous immunoglobulin.

INTRODUCTION

Kawasaki Disease is one of the most common acute febrile multisystem vasculitides of childhood and a leading cause of acquired heart disease in children[1]. It was explained first by Dr. Tomisaku Kawasaki in Japan in 1967[2]. Kawasaki disease has been reported from all over the world with the greatest incidence in Japan, reported upto 175 per 100,000 children. The annual attack rate in USA in higher in Asians as compared to non-Asian individuals. Pakistan lies in the geographical region where the incidence of this disease is 70 per 1 lac children[3]. The exact figures are unknown. The etiological agent is still unknown and no diagnostic test is available for KD. Thus diagnosis, clinical management, and research depend on a definition comprising of clinical symptoms and signs. The major advantage of timely diagnosis of Kawasaki disease is the possibility to prevent the complication of coronary artery abnormalities by timely treatment with intravenous immunoglobulin (IVIG)[3]. The present study aims to determine the spectrum of clinical features of KD and its demographic profiles, investigations, cardiac complications and effects of treatment in KD. Although KD is a well known entity in Pakistan, a very few studies have been published in this regard and the exact burden of this disease in our country is still unknown. The basic rationale of our study is to see the spectrum of clinical features of the disease, highlight the effects of IVIG used in our patients and to study the outcome and

Correspondence: Dr Shahid Mahmud, Classified Child Specialist PNS Shifa Karachi Pakistan
Email: childspec@hotmail.com
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complications of KD in Pak Emirates Military Hospital, Rawalpindi.

MATERIAL AND METHODS

This descriptive study was carried out at Paediatric department of Pak Emirates Military Hospital Rawalpindi, which is a 300 bed capacity tertiary care army referral hospital, from January 2007 to December 2011. The study population comprised of children between ages of 2 months and 12 years, reporting to Military Hospital (MH) Rawalpindi and those referred from primary or secondary care hospitals who met the diagnostic criteria for KD according to the American Heart Association and American Academy of Paediatrics guidelines[1]. Kawasaki Disease was diagnosed with fever >5 days and at least 4 out of 5 clinical features polymorphous rash, non-purulent conjunctivitis, cervical lymph node enlargement, changes of the extremities and changes of the oral mucosa. Patients were also included if aneurysm, dilatation, or ectasia of the coronary arteries were seen at echocardiography, and 3 out of 5 other clinical criteria were met (Incomplete Kawasaki disease). Children under 2 months of age were excluded from the study. All patients with documented streptococcal infection, or patients not meeting clinical criterion. All the patients meeting the inclusion criteria went through physical examination and investigations to look for any other cause of fever with rash. The children underwent investigations including complete blood count (CBC), urine examination, cardiac enzymes, erythrocyte sedimentation rate (ESR), blood culture, liver function tests, renal function tests, throat cultures, chest x-rays, and an electrocardiogram (ECG). 2-D Echocardiography was performed by an experienced pediatric cardiologist using Philips IE-33 probe s8/5 echocardiography machine to identify any coronary artery dilatation and/or aneurysms. Information collected from the children's parents

Table-I: Clinical Features of patients with Kawasaki Disease.

S. No.	Variable	No of cases (%) (n=25)
1	Age <1 year 1-5 years 5-10 years 10-12 years	 1 (4%) 17 (68%) 5 (20%) 2(8%)
2	Fever	25 (100%)
3	Eye changes	25 (100%)
4	Changes in the lips and oral cavity	24 (96%)
5	Swelling of extremities Hands Feet Both hands and feet	23 (92%) 3 (12%) 2 (8%) 18 (72%)
6	Desquamation Hands Feet Both Hands and Feet Perineal desquamation	23 (92%) 3 (12%) 2 (8%) 18 (72%) 10 (40%)
7	Rash	13 (52%)
8	Cervical lymphadenopathy	17 (68%)
9	BCG induration	7 (28%)
10	Hepatomegaly	5 (20%)
11	Joint pains	10 (40%)
12	Sensorineural hearing loss	1 (4%)
13	Urethritis	2 (8%)

and case notes by the researcher were recorded on a data sheet. The study was approved by the Research and Ethics Committee. Written informed consent was obtained from the parents of all the participants. Demographic data was obtained from children's parents including age and gender of the patient. The children were followed up in Paediatric OPD by paediatrician on regular basis and echocardiography was done if indicated. All data was analyzed using Statistical Package for Social Sciences (SPSS) version 18.0. Frequencies and percentages were taken out for the qualitative data; mean and standard deviation were taken out for the numerical variable.

RESULTS

KD was identified in 25 cases. Males were 18 and females were 7. Mean age at diagnosis was 3.7 ± 3.0 years (range 0.3-12 years). The age distribution is shown in figure which showed that majority of the cases were under 5 years of age. All of the patients had a high-grade fever for at least 5 days before admission to the hospital. Mean duration offever was 11.5 ± 3.2 days. Lymphadenopathy was cervical. Rest of the clinical findings are shown in table-I. Lab findings are shown in table-II

2-D Echocardiography was performed in all cases at admission and on follow-up as well. It was normal in 15 (60%) cases. The pattern of involvement of coronary arteries is shown in table-III with highest incidence of the coronary aneurysms seen in the left anterior descending artery. These abnormalities regressed in 7 cases on followup. Two cases had aneurysms involving 2 or more than 2 coronary arteries (figure). Giant aneurysms (>8 mm) were not seen in any patient.

Twenty four patients received intravenous immunoglobulin (IVIG) therapy at admission at a single dose of 2g/kg infused over 6 hours. All patients were put on aspirin at 80 mg/kg/ day until they became afebrile and were then switched over to low dose aspirin (3-5 mg/kg/ day). In one case we opted not to use IVIG because he presented to us in the convalescent phase and had already become afebrile. Of the 24 children who received IVIG, the fever resolved by 24 hours in 19 cases (79.1%), by 48 hours in 3 cases (12%), and by 96 hours in the remaining 2 (8%) cases after starting IVIG. Second dose of IVIG was not required in any of the cases and there was no mortality.

Table-II: Laboratory data of patients with Kawasaki disease.

S. No.	Variable	Cases
1.	Leucocytosis	15/25 (60%)
2.	Thrombocytosis	17/25 (68%)
3.	Increased CRP	21/25(84%)
4.	Increased ESR	18/25(72%)
5.	Raised ALT	8/25 (32%)
6.	Hyponatremia	3/25 (12%)
7.	Hypoalbuminemia	2/25 (8%)

Table-III: Pattern of aneurysms found in the patients with KD.

Echocardiography findings	Artery involved	No of cases (%) (n=10)	Mean Size (mm)
Aneurysms	Left anterior descending artery (LAD)	4 (40%)	2.3 ± 0.51
	Left circumflex artery (LCX)	2 (20%)	2.7 ± 0.45
	Left main stem (LMS)	1 (10%)	2.3 ± 0.32
	Right coronary artery (RCA)	1 (10%)	2.6 ± 0.47
	Both LAD and LCX	1 (10%)	3.0 ± 0.32
	LAD, LCX and RCA	1 (10%)	3.2 ± 0.41

DISCUSSION

Kawasaki disease (KD) is an acute multi system vasculitis of unknown etiology that

occurs predominantly in infants and young children. It was previously called mucocutaneous lymph node syndrome and infantile periarteritis nodosa[4]. KD has been reported from all over the world with the maximum incidence in Japanese children (upto 175 per 100,000)[5]. It has surpassed rheumatic fever as the leading cause of acquired heart disease in children according to some studies[6]. The incidence of this disease in Pakistan is still unknown. According to some international studies, males are generally affected more from KD than the females[7,8]. The present study showed a M:F of 2.751 showing a male predominance. In Japanese children, the incidence of KD is highest between 6 and 12 months of age. However, in the USA and Europe, the peak age group for KD is 18-24 months[9]. In our study, the greatest incidence was seen in children 1 to 5 yrs of age (68%). A very consistent feature in KD is fever. Fever most commonly occurs because of the elevated levels of different proinflammatory cytokines, which are thought to mediate the underlying vascular inflammation[10]. Fever was present in 100% of the patients as depicted in studies by Akhtar *et al* and Singh *et al*[2,3]. In the present study, we found that 100% of the patients with Kawasaki Disease presented with fever. Bilateral non exudative conjunctivitis is present in more than 90% of patients. Children also are frequently photophobic, and anterior uveitis may develop[11]. Study by Akhtar showed eye changes in 78% of the KD patients 2 whereas study by Burn *et al* showed involvement of eye (anterior uveitis) in 66%[12]. However our study showed that bilateral non exudative conjunctivitis was present in 100% of the cases. Cervical lymphadenopathy is the least consistent feature of Kawasaki disease[13], when present, lymphadenopathy tends to involve primarily the anterior cervical nodes overlying the sternocleidomastoid muscles. It should be noted that lymphadenopathy in KD (1 node >1.5 cm) may not always be striking and resolves rapidly toward the end of the febrile period. It can be easily missed[14]. In the present study, cervical lymphadenopathy was found in 68% of the patients and it was usually unilateral. Redness of the lips and/or tongue was very common and is often noticed by the parents themselves. Patients often present with cracked red lips and a strawberry tongue due to sloughing of filiform papillae and denuding of the inflamed glossal tissue[15]. Study by Akhtar *et al* showed that oral mucositis was present in 84% of the patients reporting to them with KD[2]. Our study showed that oral changes were present in 96% of the patients. During recovery, desquamation of the hands and feet occurs, with peeling of the skin beginning around the tips of the nails. This feature is most commonly seen during the third week after onset and persists for 1 to 2 weeks[3]. The prevalence of periungual

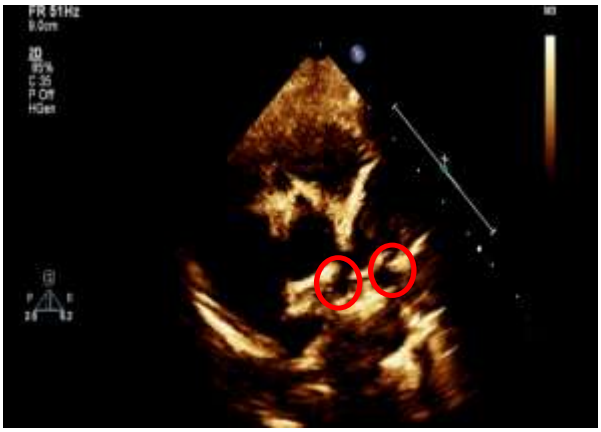

Figure: The snapshot of echocardiograph of a patient from our series showing multiple coronary artery aneurysms in Left main stem and left circumflex artery measuring 3.2 mm and 2.8 mm.

desquamation in patients with KD has been reported to vary from 68 to 98%[16]. In our study the extremity changes as well as desquamation was seen in 92% of the patients. There are no diagnostic laboratory test for KD[5]. However the common laboratary findings seen in KD include anemia, neutrophilic leucocytosis, and thrombocytosis. Thrombocytosis is usually seen during the subacute phase of theillness. This thrombocytosis has been included as a minor characteristic feature of KD by Japanese doctors[17]. In the present study thrombocytosis was seen in 68% of the patients. Nonspecific markers of inflammation, such as the erythrocyte sedimentation rate and C-reactive protein (CRP) levels, are often

elevated in KD[18] and this was confirmed by our study as seen in 72% and 84% of the patients respectively. Effect of KD on cardiovascular system is the most significant clinical problem and has been reported in upto 25% of the patients in literature[19]. The earliest manifestations occur within 10 days of onset. The most common complication in KD is the development of coronary artery dilatation and coronary artery aneurysms (CAA) which is seen in up to 25% of untreated patients but in only 5% of patients given IVIG[20]. Although coronary artery aneurysm is the most important cardiac problem as far as long term outcome is concerned, myocarditis, congestive failure, arrhythmia, and mitral and/ or aortic regurgitation have also been reported in association with KD[2,21]. About 40% patients developed CAA in our study out of which 7 patients had recovered on follow-up over a mean duration of 90 ± 30 days. In 1984 Furusho, *et al* described the role of IVIG treatment which became standard of care[22]. The benefits of higher doses of IVIG with aspirin was demonstrated in a review of 1629 patients with KD from six randomized controlled studies[23]. In our hospital, we used the same combination of IVIG (2g/kg over 6 hours) and aspirin with good outome. Twenty-four of our patients received a high dose of IVIG as a single dose. IVIG was tolerated well and no major side effects were noted in any patient. None of our patients required a second course of IVIG. There was no mortality from KD in our series. Mortality rates from KD vary from 0.08% in Japan to 3.7% in the UK[24]. Aspirin decreases the intensity of vasculitis in acute stage of illness and provides inhibition of platelet aggregation. Aspirin does not decrease the risk of coronary artery disease. However, the dose may affect the duration of fever[25]. We used aspirin at 80 mg/kg/d in all our cases until the patient became afebrile for 48 hours and then shifted to 3-5 mg/kg/day until the inflammatory markers returned to normal (CRP and platelet count). In cases where patients had developed CAA, the low dose aspirin was continued with regular followups and echocardiographs.

CONCLUSIONS

KD is now fast emerging as one of the important cause of acquired heart disease. The disease is probably under diagnosed in most developing countries and requires a high index of suspicion. The peak age was between 1-5 years. Fever was seen in all cases of KD. There is no definitive laboratory test for a diagnosis of KD. Cardiac aneurysms were found in 40% of the cases. IVIG and aspirin are the main modalities of treatment. There was no mortality in our series.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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