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Saleem Akhtar

Aga Khan University, saleem.sadqani@aku.edu

Muhammad Matloob Alam

Aga Khan University, matloob.alam@aku.edu

Mehnaz Atiq Ahmed

Aga Khan University, mehnaz.atiq@aku.edu

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Cardiac involvement in Kawasaki disease in Pakistani children

Saleem Akhtar, Muhammad Matloob Alam, Mehnaz Atiq Ahmed

Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan

ABSTRACT

Introduction : Coronary artery involvement is the most dreaded long-term complication of Kawasaki disease. Our aim was to look at the pattern of cardiovascular involvement in Pakistani children admitted with Kawasaki disease.

Methods : This study included children admitted with Kawasaki disease at the Aga Khan University Hospital Karachi over a period of 14 years from January 1997 to December 2010. Information gathered included patient demographics, clinical features, investigations, echocardiographic findings, treatment and follow-up. Those with coronary artery involvement on initial echocardiogram remained on long-term follow-up with clinical examination and echocardiogram.

Results : A total of 56 patients were admitted. (Mean age at diagnosis 33 ± 30 months, age range 2 months to 9 years). 18% of patients had incomplete features. Twenty-five percent (14/56) patients presented after 10 days of fever. Cardiac examination was normal except for tachycardia. Abnormal coronary arteries were seen in 23 patients (41%) - left main coronary artery in 23 (41%), left anterior descending and right main coronary artery in 20 (36%), circumflex branch in 17 (30%). Risk factors for cardiac involvement were male sex, fever >10 days duration at the time of initial presentation and neutrophil percentage >75% in the initial white blood cell counts. Fifty four of 56 cases received intravenous immunoglobulin (IVIG), Seventy-five percent of the patients received IVIG within 10 days of illness. Mean duration of follow-up was 2.5 years. Eight percent of the patients still continue to have abnormal coronaries. There was no mortality.

Conclusions : A higher incidence of coronary artery involvement was found in our study. Presentation after 10 days of illness increases the risk of coronary artery involvement. High index of suspicion among the general pediatricians about the disease can possibly be helpful for early referral and treatment.

Keywords : Coronary aneurysms, coronary ectasia, Kawasaki disease

INTRODUCTION

Kawasaki disease is an acute, self-limiting disease of unknown etiology.^[1] It is characterized by vasculitis involving small and medium-sized vessels of various organs with striking predilection for the coronary arteries.^[2,3] It was first described in Japan by Tomisaku

Kawasaki.^[4] It is now known to occur all around the world and in children of all races.^[1] It is the leading cause of acquired heart disease in Japan, Europe and the USA.^[5] Average annual attack rate in Japan in 1997-1998 was 112 per 100,000 cases for children under 5 years of age.^[6] The annual attack rate in USA is higher in Asians compared with non-Asians.^[7] Although Kawasaki disease is not unknown in the Indian subcontinent,^[8-10] and Pakistan, no study has been published from Pakistan. We conducted this study to evaluate the clinical features at presentation and pattern of cardiac involvement in Pakistani children with Kawasaki disease.

MATERIALS AND METHODS

This is a descriptive, observational noninterventional

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Address for correspondence: Dr. Saleem Akhtar, Department of Pediatrics and Child Health, Aga Khan University Hospital, PO Box 3500, Karachi- 74800.
E-mail: saleem.sadqani@aku.edu

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retrospective analysis. The medical records database of the Aga Khan University Hospital was searched for children admitted with the diagnosis of Kawasaki disease. Total duration of study was 14 years (January 1997 to December 2010). All patients who met the criteria for Kawasaki disease according to the American Heart Association and American Academy of Pediatrics guidelines were included in the study.^[11] Complete Kawasaki disease was diagnosed with fever ≥ 5 days and at least four of the five principal clinical features: polymorphous rash, nonpurulent conjunctivitis, cervical lymph node enlargement, changes of the extremities and changes in the oral mucosa. Patients with coronary artery involvement but less than four criteria were labeled as incomplete Kawasaki disease when other diseases were excluded.^[11]

Clinical notes were carefully reviewed with respect to patient demographics, clinical features, investigations, echocardiographic findings, treatment and follow-up. Initial echocardiography was performed by an experienced pediatric cardiologist on GE vivid 7 and Philips Sonos 5500 echocardiographic machines. The procedure was performed in the standard way using 7 Hz probe for smaller children and 3 Hz for older children. Information sought on 2D, color flow and Spectral Doppler echocardiography included left ventricular dimensions and function, valve regurgitation, coronary artery ectasia or aneurysm and pericardial effusion. If no coronary artery involvement was present at the time of initial echocardiogram, repeat echocardiography was done at discharge, at 3–4 weeks and 6–8 weeks. Those with coronary artery involvement on initial echocardiogram remained on long-term follow-up with clinical examination and echocardiogram. As there is no data of coronary artery dimensions in Pakistani children, definition of coronary lesions was based on standards published by Nakano *et al.*^[12] Coronary artery dimensions were indexed to body surface area. When necessary, we used chloral hydrate to sedate children to ensure a detailed study.

Data was analyzed by using SPSS (version 16.0). Results are presented as mean \pm standard deviation for quantitative variables and no. (%) for qualitative variables. Difference in mean was assessed by using sample t-test. *P*-value less than 0.05 was considered as statistically significant. Outcome was presence or absence of coronary artery involvement.

RESULTS

A total of 56 patients who fulfilled the criteria for Kawasaki diseases were enrolled in the study. Mean age at diagnosis was 33 ± 30 months, age range being 2 months to 9 years. Most of the patients (77.6%) were less than 5 years of age. The male to female ratio was 1.33:1. Mean weight was 13.5 ± 7.3 kg. Fifty-five percent of the cases were seen in winter and spring. Seventy-five percent of the cases presented within 10 days of illness while the remaining (25%) cases

presented after 10 days of fever. The clinical features are summarized in Table 1. Mean duration of fever at the time of admission was 9 ± 4 days. Mean duration of hospital stay was 6 ± 2 days. We divided the study duration into early (1997–2001), intermediate (2002–2006) and late experience (2007–2010). Forty-eight percent (48%) of the cases were seen during the later part of the study (2007–2010), while 30% cases were seen in middle part of the study. Two-thirds of the cases (65%) presented in the winter and spring seasons.

Eighteen percent of the cases had incomplete Kawasaki disease. Children less than 1 year of age were more likely to have incomplete Kawasaki disease (*P*-value = 0.001). Additional clinical features seen consisted of irritability (71%), gastrointestinal symptoms including diarrhea and vomiting (37%), edema (22%), joint involvement (22%) and signs of meningeal irritation (6%).

Apart from sinus tachycardia during sleep, which was present in 90% of the cases, the remaining of the cardiovascular examination was normal. No patient had gallop rhythm, decreased heart sounds or murmur on auscultation.

Blood counts, erythrocyte sedimentation rate and C-reactive proteins were obtained in all patients. Forty-one percent of the children had anemia for age, 84% had neutrophilic leukocytosis and 86% had thrombocytosis. Erythrocyte sedimentation rate and C-reactive proteins were elevated in 94% of the cases. X-ray chest was normal in all patients. Electrocardiogram showed sinus tachycardia in 90% of the cases with no evidence of myocardial ischemia or arrhythmia.

Echocardiography was done in all patients at the time of admission. Abnormal coronary arteries were seen in 41% of the cases based on the cut-off values mentioned by Nakano *et al.* Pattern of coronary artery involvement was as follows: left main coronary artery 41% (23/56), left anterior descending and right main coronary artery (20/56) 36%, circumflex branch in (17/56) 30%. Majority (94%) of the patients had mild dilatation or ectasia of coronary arteries. 3 patients (5.6%) had evidence of aneurysm (small to moderate sized) formation on initial echocardiogram. One patient had a giant aneurysm in the right coronary artery. Left ventricular function was normal in all patients. Three patients had trace-mild mitral regurgitation, which resolved on follow-up echocardiogram. One-third of the patients had trace to mild pericardial effusion. Risk factors for cardiac involvement identified in our study were male sex, fever >10 days duration at the time of initial presentation and neutrophil percentage $>75\%$ in the initial white blood cell counts [Table 2].

IVIG was administered to 54 (96%) cases. Seventy-five percent of the patients received IVIG within 10 days of

illness. Rest of the patients (21%) received IVIG after the 10th day of illness. Decision to give IVIG after the 10th day of illness was based on persistent fever along with raised inflammatory markers. In four cases, the diagnosis of Kawasaki disease was made before the patient came to our unit. These cases presented in the subacute phase of the disease when skin peeling was picked up. Two of these patients (4%) did not receive IVIG. Dose was of 2 g/kg of body weight. All patients received high-dose aspirin (80–100 mg/kg) during the acute phase of the illness. Ninety-eight percent of the patients became afebrile after IVIG infusion. One patient required a 2nd dose of IVIG. No patient was given steroids. Aspirin was switched to antiplatelet dose after 48–72 h of afebrile period. Additional dipyridamole was prescribed to two and clopidogrel to one patient, until normalization of coronary artery aneurysm. One patient with giant coronary aneurysm was kept on warfarin for 6 months, after which the patient was lost to follow-up as the family moved abroad.

Eighty percent of the patients came for follow-up. Patients who were lost to follow-up included patients who belonged to other provinces of Pakistan and went back to their native town after acute illness and are being followed in other centers. One patient came from Canada and while staying in Pakistan developed Kawasaki disease. He went back to Canada after acute treatment and is being followed there. Mean duration of follow-up was 2.5±2 (range 4months to 13 years) years as majority of our patients were seen in the later part of the study. None of the patients developed symptoms of myocardial ischemia during follow-up. Seven percent (4/56) of the patients still continue to have abnormal coronaries. There was no statistically significant correlation between persistence of coronary artery involvement with no use of IVIG. There was no association between persistent

fever and persistence of coronary artery involvement. Coronary arteries returned to normal in the remaining. No mortality, recurrence and familial involvement were seen in the study population.

DISCUSSION

Kawasaki disease occurs in children of all races, but is more common in Japan. The incidence of Kawasaki disease is increasing worldwide.^[13] The causative agent still remains elusive.^[14] No study addressing cardiovascular involvement in Kawasaki disease has been published from Pakistan.

Cardiac involvement is the most important feature of Kawasaki disease. Cardiac involvement has been variably reported in up to 25% of the cases.^[15,16] Coronary artery involvement was seen in 41% of our cases. Coronary artery involvement is higher than previously reported in other series.^[16] However, this could possibly be explained partly by the higher number of incomplete cases (18%), younger age (28.6%) and delayed presentation (25%). Coronary artery involvement is higher in children who have incomplete features.^[16] The number of patients presenting after the 10th day of illness is high in our study (25%). This can be because of the higher number of incomplete cases and lack of awareness among general pediatricians about the disease. Pattern of coronary involvement in our study group is consistent with the one previously reported. 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.

Although coronary artery involvement is among the most important cardiac lesion so far as long-term outcome is concerned, cardiac involvement is by no means limited to this.^[17] Pericarditis, myocarditis, endocarditis and conduction disturbances have all been reported in patients with Kawasaki disease.^[18,19] These findings are self-limited most of the time. Rarely, these patients can present with overt heart failure due to underlying myocardial involvement. There was no involvement of myocardium in our series of patients. Three of our patients had trace to mild mitral regurgitation, which improved during follow-up studies. This is consistent with the studies reported previously.^[5] Some of our patients also had trace to pericardial effusion diagnosed on echocardiography. Pericardial effusion resolved without any sequelae as reported in the literature.

These risk factors for cardiac involvement have been reported previously.^[5,7] On follow-up, coronary artery dimensions normalized in the majority of our patients. These finding are consistent with the internationally reported literature. Most of our patients had small to moderate-sized aneurysms, which are more likely to

Table 1: Clinical features at the time of presentation

Clinical features	Number (% age of cases)
Fever	100
Rash	85
Oral cavity changes	84
Extremity changes	79
Eye changes	78
Cervical lymphadenopathy	43

Table 2: Risk factors for coronary artery involvement

Risk factors	P-value	Odds ratio	Confidence interval
Male sex	0.017	5.82	1.25-12.77
Age <1 year	0.9	0.86	0.3-3.02
Fever >10 days	0.04	4.1	1.0-9.88
Hemoglobin <10 g/dL	0.18	1.77	0.7-6.1
Platelets >500,000/mm ³	0.9	0.86	0.33-3.0
WBC count >15000/mm ³	0.12	2.4	0.2-3.0
Incomplete Kawasaki disease	0.9	0.15	0.2-3.80
Neutrophils >75%	0.05	5.7	0.3-3.0

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regress in size.^[20] Small to moderate-sized aneurysms are very likely to regress and have a good prognosis in childhood.^[20] A few of our patients have grown into adulthood and are doing fine. However, it is premature to say whether these patients are at increased risk for premature coronary artery disease.^[21] Long-term studies are needed for this.

The number of patients seen in the later part of study is higher than those seen in the early and middle parts of our study. Whether this increase is due to increasing number of cases or increased awareness among pediatricians about this disease is not known.

CONCLUSIONS

Coronary artery involvement was found to be higher in our study. Presentation after 10 days of illness increases the risk of coronary artery involvement. A high index of suspicion among the general pediatricians about the disease can possibly be helpful for early referral and treatment.

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