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CARDIAC SEQUELAE OF KAWASAKI DISEASE IN ISFAHAN, IRAN

A.R. NIKYAR, M.D.,* R. KORDYDARIAN, M.D., AND R. IRANPOUR, M.D.*****

From the Department of Pediatrics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran.

ABSTRACT

Kawasaki disease is one of the major causes of acquired heart disease of children in developed countries. This study was performed to determine the frequency of cardiac sequelae of kawasaki disease and related risk factors based on a descriptive cross-sectional study between 1994-1999 in the pediatric ward of Al-Zahra Hospital of Isfahan.

Out of 45 patients, 29 were male (64.4%) and 16 were female (35.6%) with a sex ratio of 1.8 ($p<0.05$). Five patients suffered from pericardial effusion (11.1%), 6 patients had mitral valve insufficiency (13.3%) and 10 patients (22.6%) had coronary artery aneurysms (CAA). Seven and 3 cases of these 10 CAA cases were male and female, respectively, with a sex ratio of 2.3 ($p<0.05$). CAA's were less in patients who received intravenous immunoglobulin (IVIG) in the first 10 days than untreated cases or cases who were treated later ($p<0.05$). CAA's persisted only in 2 patients after the convalescent period of disease and a new case of CAA which did not exist in the acute phase was detected. In conclusion, CAA's in this study were higher than worldwide reports. Early diagnosis and treatment with IVIG are necessary for prevention of cardiac involvement in kawasaki disease.
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INTRODUCTION

Kawasaki disease is a diffuse vasculitis of unknown etiology and is one of the major causes of acquired heart disease of children in developed countries.[1,2] The presence of cardiac involvement affects the prognosis of the disease.[2] Diagnosis of kawasaki disease is clinical and according to American Heart Association diagnostic criteria is as follows: persistent fever at least for five days, plus four of these five clinical findings; 1) changes in extremities, 2) polymorphous exanthem, 3) bilateral conjunctivitis, 4) changes in lips and oral cavity and 5) cervical lymphadenopathy.[3] Atypical cases have been reported, especially in infants less than 6 months of age (with less than 4 of these 5 major criteria). In each febrile patient who was affected with three major criteria, kawasaki disease can be considered if CAA is detected by echocardiogram or coronary angiography.[4] Cardiovascular complications are mostly present in the acute phase of disease and are the major cause of morbidity and mortality of kawasaki patients.[5]

Cardiac involvement inculdes pericardial effusion, myocardial inflammation (up to 50% of patients) and coronary artery abnormalities, usually developing later than 10 days after onset of illness.[6] Coronary artery abnormalities (ectasia or aneurysms) were observed in 20-25% of untreated patients.[7] A poor prognosis is observed in patients who are affected with large aneurysms (the largest internal diameter at least 8 millimeters) and the most frequent risk of thrombosis or stricture of coronary arteries or myocardial infarction are observed in

*Correspondence: A.R. Nikyar, M.D., Pediatric cardiologist, Associate Professor of Pediatrics, Isfahan University of Medical Sciences.
**Associate Professor of Pediatrics, Isfahan University of Medical Sciences.
***Assistant Professor of Pediatrics, Isfahan University of Medical Sciences.

this group.[4] Large aneurysms are less likely than small ones to regress spontaneously. Aneurysms are usually manifest during 1-3 weeks after onset of fever and presentation after 5 weeks is unusual. Long term follow-up with echocardiography and angiography reveals that 50% of aneurysms regress spontaneously during 5-18 months and the rest also decrease in size.[8]

Because there has been no conclusive study in Iran concerning cardiac involvement in kawasaki disease and due to it's persistent sequelae in some cases, we decided to survey the hospitalized kawasaki patients of Al-Zahra Medical Center, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran in view of cardiac sequelae and related risk factors and to follow all patients until the convalescence period of disease.

MATERIAL AND METHODS

A descriptive cross-sectional study was done on kawasaki patients who were hospitalized in the pediatric ward of Al-Zahra Hosptial, Isfahan. Inclusion criteria were existence of diagnostic clinical signs and symptoms consisting of 5 days fever in addition to 4 of 5 major findings. Meanwhile, any patient with fever plus 3 major findings was included as well, if coronary vessel involvement was confirmed by echocardiography.

Clinical manifestations, laboratory data, and cardiac and non-cardiac sequelae of the disease and personal characteristics of patients including age, sex, type of treatment, time of beginning of intravenous immunoglobulin (IVIG) or aspirin therapy and duration time of response to treatment were all recorded. Aspirin was started in a dose of 100 mg/kg/day and IVIG in a dose of 2g /kg as a single dose.

For all patients echocardiographic evaluation was done and repeated weekly in the first 2 months. After the convalescent phase (18 months later), echocardiogram and physical examination was repeated for all patients. Patients who did not participate in follow-up echocardiographies were excluded.

In all echocardiographies a 5-MHZ mechanical sector scanner was used. In two-dimentional echocardiography, pericardial effusion, ventricular function, cardiac valves and coronary arteries were evaluated. A coronary artery with internal diameter of more than 3 and 4mm was considered abnormal in children under 5 years old and greater than 5 years old, respectively. If the diameter of one segment of the artery was 1.5 times greater than that of adjacent segments or if obvious irregularity was observed, the artery would also be considered as abnormal.

Collected data were analysed with SPSS software (windows operating system). Chi-square test and Fisher's exact test were used for assessment of frequency of cardiac sequelae in term of sex, age, time of receiving IVIG, WBC count, C-reactive protein and platelet count. Mantel-Hanzel test was used for determining relation of frequency of aneurysms with erythrocyte sedimentation rate (ESR). P values less than 0.05 were considered statistically significant.

RESULTS

Between 1994 and 1999 cross-sectional serial echocardiographic examination was carried out on 45 of 47 children in whom a diagnosis of kawasaki disease had been made at the onset of their illness. There were 29 boys and 16 girls (male to female ratio: 1.8) with significant difference ($p<0.05$).

The age of onset of the disease ranged from 6 months to 16 years. The most frequent age group was 1 to 6 years (36 cases, 80%) in contrast with age groups less than 1 year and more than 6 years old (9 cases, 20%), that according to chi-square test this difference was significant ($p<0.001$). One out of 45 patients had pleural effusion (2.2%). Five children had hydrops of the gallbladder (11.1%) and one had encephalopathy (2.2%).

Echocardiographic findings during the acute phase of disease included pericardial effusion (5 cases, 11.1%), mitral regurgitation (6 cases, 13.3%) and CAA (9 cases, 20%). One case who had no complication in the acute and subacute phase was affected with CAA in the convalescent period.

Of 10 (22.2%) CAA, 6 subjects (60%) had only left coronary artery involvement, 1 subject (10%) had right coronary artery involvement and in 3 subjects (30%) both left and right coronary arteries were affected. Diameters of aneurysms in these ten patients were as follows: 1 case, 4mm; 4 cases, 5mm; 2 cases, 6mm; 1 case 7mm, and 2 had 9 mm aneurysms. Seven out of 10 aneurysms were in boys (male to female ratio: 2.3) with a significant difference ($p<0.05$).

Table I shows relationships between treatment with IVIG and existence of CAA. Five out of 45 patients did not receive IVIG due to unavailability of IVIG or being referred after elimination of signs and symptoms. Six patients received IVIG 10 days after onset of disease.

The frequency of CAA in the groups who received IVIG in the first 10 days was significantly lower than groups not receiving IVIG or receiving IVIG after 10 days ($p<0.05$). If we considered the non-IVIG group and the IVIG group after 10 days as a single group (11 cases) and compare them with the IVIG group before 10 days (34 cases), the frequency of CAA is significantly higher than in the first group (45.5% versus 14.7%), with a $p<0.05$.

Table II shows relationships of WBC count, C-reactive protein (CRP) and ESR with existence of CAA. A WBC count>20.000 per mm^3 was a risk factor for for-

Table I. Numbers of patients and percentage of patients with coronary artery aneurysm based on IVIG therapy.

Group / Coronary artery aneurysm	No (%) of patients	No (%) of patients with IVIG before 10 days	No (%) of patients with IVIG after 10 days	No (%) patients without IVIG
Positive	10 (22.2)	5 (14.7)	4 (66.7)	1 (20)
Negative	35 (77.7)	29 (85.2)	2. (33.3)	4 (80)

Table II. Numbers and percentage of patients with coronary artery aneurysm based on laboratory data.

Group / Parameters	No (%) of patients	No (%) of patients with aneurysm	No (%) of patients without aneurysm	*P* Value
WBC count >20,000/mm^3	15 (33.3)	7 (15.6)	8 (17.8)	
WBC count <20,000/mm^3	30 (66.7)	3 (6.7)	27 (60)	$p < 0.01$
CRP Positive	31 (77.5)	9 (22.5)	22 (55)	
CRP Negative	9 (22.5)	0 (0)	9 (22.5)	$p > 0.05$
ESR <50	7 (15.6)	0 (0)	7 (15.6)	
ESR 50-100	13 (28.9)	1 (2.2)	12 (26.7)	$p < 0.05$
ESR >100	25 (55.5)	9 (20)	16 (35.5)	

mation of aneurysms ($p<0.01$). This difference in regard to CRP was not significant ($p>0.05$) but regarding ESR it was significant ($p<0.05$) and according to the Mantel-Hanzel test there was a liner relation ($p<0.05$).

Five out of 45 patients had pericardial effusion, 4 of these 5 patients also had CAA, so there was a significant association between pericardial effusion and CAA ($p<0.01$).

Follow-up of 45 patients in the convalescent period with repeat echocardiographic evaluation revealed that all patients with any sequelae such as mitral valve insufficiency, pericardial effusion and CAA were improved except for 2 patients who had large CAA's.

DISCUSSION

Kawasaki disease often affects children under 5 years-old and boys are affected more.[8] Studies confirm this male gender predominance. The male to female ratio reported from several countries is as follows: Japan (1.4), the United States (1.4), Canada (1.7), England (1.3), Korea (1.8), Germany (1.5) and Finland (1.2).[9] In our study the male to female ratio was 1.8. The frequency of CAA in studies of Suzuki, Tizard, Schulman and Kato were 28, 18, 16 and 15 percent, respectively.[10-13] In our study this figure was 22.2%. The frequency of CAA in IVIG-treated patients in studies by Prak and Furusho were 4% and 2.5% respectively[3,14] and in ours was 14.7% which may indicate a weaker prophylactic effect of IVIG for CAA in our study. The percentage of patients with CAA decreased with IVIG therapy from 20% to 3-4 percent[8] and in our study this difference was significant although not the same as other reports.

The frequency of pericardial effusion in this study (11.1%) resembled Tizard's study of 11%[11] but was less than Kato's study (35%).[13]

Mitral valve disease in this study had occurred in 13.3% in contrast with that reported by Kato (1%) and Tizard (4%).[11,13]

Clinically recognizable myocarditis, occasionally with congestive heart failure, is commonly manifested by tachycardia out of proportion to the degree of fever, a gallop rhythm and arrhythmia.[8] In our series none of the patients had these signs. In a similar study in a pediatric hospital in Riyadh, myocarditis was not reported in 29 Kawasaki patients,[15] although some studies have reported up to 50%.[6]

We revealed that male gender, WBC count more than 20,000 per mm,^{3} elevated ESR, pericardial effusion and lack of initiation of IVIG in the first 10 days of disease are risk factors for occurrence of CAA and these patients must be followed-up carefully.

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