ORIGINAL REPORT

Association of Sterile Pyuria and Coronary Artery Aneurysm in Kawasaki Syndrome

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Abstract- Kawasaki disease (KD) is an inflammatory multiorgan disease of unknown etiology. The most dramatic organ involved is the heart. There were a few studies about cardiac involvement and sterile pyuria. This study guides to determine if sterile pyuria is associated with coronary artery aneurysm (CAA) in KD patients and to consider it as a predicting factor for coronary artery involvement. Forty seven patients with KD were studied by echocardiography in admission and one month later. Urine analysis, complete blood count, erythrocyte sedimentation rate and C-reactive protein were measured in admission. Data were analyzed using SPSS-14 software. Patients' age was ranged from 13 month to 7 years old (mean age of 3.43±1.54 years). Thirty patients (63.8%) were male and 17 patients (36.1%) were female. Cardiac involvement was detected in 32 patients (68%) using echocardiography, of which CAA was reported in 8 cases (17%). Six of CAA (75%) were in association with sterile pyuria, although it was statistically insignificant (P>0.05). Although the majority of patients with CAA had sterile pyuria, this association is not statistically significant, thus it couldn't be considered as a predicting factor for CAA.

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Introduction

Kawasaki disease (KD), an acute febrile vasculitis of unknown etiology, was first described in late 1960's by Tomisaku Kawasaki in Japan. It occurs worldwide and primarily affects younger children. Many studies searching for the etiologic agent of KD have not consistently identified a specific etiology, but there are some hypothesis to support infectious agents and superantigens (1-4).

Kawasaki disease is a systemic medium vessel vasculitis, which its primary morbidity is coronary artery involvement. It is the most common cause of acquired heart disease in children in the United States, United Kingdom, and Japan. Approximately 20-25% of untreated patients have been reported to developed coronary artery aneurysms in the first 2nd-3rd week of illness which are best detected by two-dimensional echocardiography (5-7). KD results in vasculitis of the large to medium-sized arteries; weakening of the arterial wall leads to dilatation and aneurysm formation.

Myocarditis is the most common noncoronary complication and is present in at least 50% of patients with acute KD. Myocarditis is often clinically manifested by tachycardia that is excessive for the degree of temperature elevation. Electrocardiographic (ECG) changes such as a prolonged PR interval, ST-T segment changes, and decreased voltage of R waves may indicate the presence of myocarditis.

Pericarditis with pericardial effusion occurs in about 25% of patients in the acute phase. Valvular disease, predominantly mitral regurgitation, has been seen in about 1% of patients and occasionally has required valve replacement (8). 1-10 % of all KD patients had mitral valve regurgitation (8) which appeared primarily during the acute or subacute stage.

An Iranian study (9) showed of 61 pediatric cases of Kawasaki disease, 41cases (69%) did not have any sign of cardiac involvement. Coronary artery aneurism was detected in8 cases (13%). Pericardial effusion was seen in 11%. There were ECG changes and cardiomegaly each in 8% of patients. Mild mitral regurgitation was

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seen in 10%. In a Japanese study (10), of the 12966 patients 7489 males and 5477 females, the incidence rates of cardiac lesions were 27.2% in the acute stage and 10.1% a month after onset. In females, the rates were 16.7% and 5.2%, respectively. The incidence rates of cardiac lesions were highest in the youngest age group (<6 months old) both in the acute stage and 1 month after onset. The rates decreased with increasing ages. Although frequency of giant aneurysms was not high at the acute stage, it did not decrease 1 month after onset.

The disease course is divided to three stage: acute, sub acute and chronic (11,12).

Studies of risk factors associated with coronary artery involvement showed that patients' age (<1yr and >9 yrs), male gender, Asian race (13), laboratory abnormalities (such as higher white cell or neutrophil count, lower platelet count, higher C-reactive protein, higher erythrocyte sedimentation rate, lower serum albumin, and lower hemoglobin or hematocrit), and treatment delay have been inconsistent in their association with coronary artery abnormalities (14).

But progressively other risk factors are determined, for instance association of sterile pyuria and coronary artery aneurysm was reported in a study by Mason in 1991 (15). According to our knowledge, this is the only article assessed this association available in the literature. This study was conducted to determine if sterile pyuria is associated with the formation of coronary artery aneurysm (CAA) in KD patients and consider it as a predicting factor for coronary artery involvement.

Materials and Methods

This prospective study was performed at Qom Pediatric University Hospital (Qom-Iran) from December 2007 to November 2008. Forty seven patients with Kawasaki disease, who were referred from Qom and Markazi state hospitals, were analyzed to evaluate the characteristics, clinical manifestations, cardiac involvements, laboratory data and method of management. This study was approved by Clinical Research Development Center and Ethics Committee of Qom University of Medical Science. All parents gave written informed consent before participation.

The criteria to confirm the diagnosis of KD are listed in table 2 (16). Echocardiography was performed by one cardiologist to determine cardiac involvement.

We adopted two-dimensional echocardiography for evaluation of coronary aneurysms beginning in 1979 using an ESOATE MY Lab 30 with a 5-MHz transducer. Serial echocardiograms were taken at least four times during the acute stage of the illness: on admission, at 7 days of illness, and at 2 and weeks of illness. The two-dimensional echocardiographic examination included display of the main trunk, anterior descending and circumflex branches of the left coronary artery, and the main and distal segments of the right coronary artery by standard manipulation.

The echo density in the coronary arterial wall or in the region of an aneurysm was investigated further for calcification and changes in tissue characterization compared with a normal portion of the arterial wall by the method of changing the attenuation of the echo gain. CAA was considered if coronary artery diameter was >3mm in patients lesser than 5 years old and >4mm in patients greater than 5 years old, if coronary artery diameter was 1.5 times of adjacent coronary artery and/or if coronary artery lumen was irregular on echocardiography. Giant aneurysm was defined as coronary artery diameter more than 8mm (17). Left ventricular function and the presence of pericardial effusion were also investigated. Valvular regurgitation and the function of the cardiac valves were determined by use of Doppler echocardiography. Repeat two-dimensional echocardiographic studies were performed at follow-up.

Data were analyzed using SPSS-14 software.

Results

From December 2007 to November 2008, 47 KD patients were admitted in our hospital. Since the only pediatric cardiology department exists in this University Hospital in Qom, these patients represent an accurate number of KD patients reported in Qom and Markazi state in this period the study data are listed in table 1. Patients' age was ranged from 13 month to 7 years old with mean age of 3.43±1.54 years. Forty one patients (87.2%) were one to five years old. Thirty patients (63.8%) were male and 17 patients (36.1%) were female (male to female ratio: 1.7).

Fever was detected in all 47 patients. Patients' signs and symptoms are showed in table 3.

All patients had erythrocyte sedimentation rate (ESR) more than 40 mm/hour. Sterile pyuria (white blood cells in urine with negative urine culture) was reported in 32 patients (68%) and thrombocytosis in 39 patients (82.9%).

Table 1. Demographic & Laboratory data of the patients.

No.	age	gender	Sterile pyuria	WBC NO in U/A	High plt	CRP Mg/dl	Aneurysm
1	13m	f	no	0	+	15	-
2	17m	m	+	6	-	20	-
3	18m	m	+	5	+	20	-
4	21m	f	+	5	-	10	-
5	24m	m	+	7	+	15	-
6	24m	m	no	0	+	30	-
7	28m	m	+	11	-	20	-
8	29m	f	+	6	+	20	+
9	32m	m	no	0	+	25	+
10	33m	m	+	5	+	15	-
11	36m	m	+	8	+	15	-
12	36m	m	no	0	-	10	-
13	37m	f	+	7	+	20	-
14	38m	m	no	0	+	20	-
15	38m	f	+	6	-	25	+
16	40m	m	+	15	+	25	-
17	40m	m	no	0	+	30	+
18	42m	m	+	7	+	30	-
19	44m	f	+	7	+	10	-
20	44m	m	no	0	+	15	-
21	44m	m	+	6	+	20	-
22	44m	f	+	5	+	15	-
23	45m	f	+	5	+	25	-
24	45m	m	no	0	+	40	+
25	46m	m	+	8	+	25	-
26	45m	m	+	7	-	15	-
27	47m	m	+	7	+	15	-
28	47m	f	no	0	+	30	-
29	47m	f	+	12	+	30	+
30	48m	m	+	6	-	25	-
31	48m	f	+	5	+	20	-
32	48m	m	no	0	+	15	-
33	50m	m	+	٧	+	15	-
34	50m	f	+	5	+	20	-
35	53m	m	+	5	+	15	-
36	55m	m	no	0	+	20	-
37	57m	f	+	8	+	20	-
38	57m	m	+	5	+	25	-
39	58m	m	+	6	+	20	-
40	60m	f	no	0	+	15	-
41	60m	m	+	5	+	15	-
42	64m	m	+	7	-	15	+
43	69m	m	no	0	+	25	-
44	72m	f	+	6	+	15	-
45	79m	f	no	0	+	25	-
46	80m	m	+	7	+	20	+
47	84m	f	no	0	+	20	-

m= month

Table 2. Criteria to confirm the diagnosis of KD.

fever ≥5 days unresponsive to antibiotics, and at least four of the five following physical findings with no other more reasonable explanation for the observed clinical findings:
Bilateral bulbar conjunctival injection without exudates
Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
peripheral extremity changes
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem
cervical lymphadenopathy (at least one lymph node ≥1.5 cm in diameter)

Cardiac involvement was detected in 32 patients (68%) using echocardiography, of which 10 patients (21.2%) had mitral regurgitation, 8 patients (17%) had CAA (in 6 patients right and left coronary artery and in 2 patients only left coronary artery involvement), 5 patients (10.6%) had tricuspid regurgitation, 5 patients (10.6%) had ECG changes and 4 patients (8.5%) had pericardial effusion.

CAA was detected in seven patients in their first echocardiography and in one patient in the second echocardiography performed one week later. Among 8 patients with CAA, 6 patients (75%) had sterile pyuria. Although this association was statistically insignificant (P=0.6).

There wasn't significant correlation between patient's age and gender with aneurismal formation (P>0.05).

In abdominal sonography, gall bladder involvement (including wall thickening, sludge, etc.) was reported in 13 patients (27.6%).

Treatment used in the patients was a varying combination of IVIG and aspirin.

Dilated coronary artery was regressed in five patients (62.5%) in the second echocardiography, performed four weeks later, but it was persisted in the remaining for at least two months.

Discussion

Our knowledge about association between coronary involvement and sterile pyuria is limited. This study guides to determine if sterile pyuria is associated with the formation of CAA in KD patients and to consider it as a predicting factor for coronary artery involvement.

Kawasaki disease most commonly occurred in patients younger than 5-year-old, with peak incidence of 3-5 months of age in females and 2 peaks occurring in males; at 3-5 months and at 9-11 months of age, 82% of cases are less than 4-year-old. It affecting males 1.3 times than girls, as mentioned in the literature (4,5,18).

In this study, patients' age was ranged from 13 month to 7 years old with mean age of 3.43±1.54 years. Forty one patients (87.2%) were one to five years old. Thirty patients (63.8%) were male and 17 patients (36.1%) were female (male to female ratio: 1.7). These discrepancies may be due to environmental and genetically differences between study populations.

Clinical presentation and paraclinic data was same as similar studies (19-22).

Sterile pyuria is one of the most common manifestations of Kawasaki disease and is seen in 33% to 63% of patients in the acute phase (18,23). In the present study, sterile pyuria was reported in 68% of cases, which resembles that of other studies.

Table 3. Clinical manifestation of the patients.

Signs & Symptoms	**No. (%)**
Fever	47 (100)
Oral changes	28 (59.5)
Extremities' changes (erythema, edema and desquamation)	37 (78.7)
Rash (maculopapular, scarlatiniform and erythema multiform rashes)	26 (55.3)
Cervical lymphadenopathy	34 (72.3)
Periungual desquamation	16 (34)

The primary and most serious morbidity of KD is coronary artery involvement and is the leading cause of acquired heart disease in some countries (5,24).

Yeo *et al.* in a study on 136 KD patients younger than 1-year-old concluded that incomplete clinical manifestations (OR=0.493, 95% CI=0.293-0.829, *P*=0.007) and a longer duration of total fever (OR=1.405, 95% CI=1.092-1.808, *P*=0.008) are significantly associated with the development of CAA in these patients. Therefore, these patients should be monitored for incomplete KD, especially if unexplained fever continues, and treatment to shorten the duration of total fever should be initiated (25).

Mason *et al.* studied on 123 patients with KD and reported the higher incidence of coronary artery involvement in patients with sterile pyuria (15). In our study, CAA was reported in 17% of patients, of which 75% had concomitant sterile pyuria, although it was statistically insignificant (*P*>0.05).

Unfortunately, there are a few studies in this field, so we advise evaluation of this association in all Kawasaki patients and answer to this question: do sterile pyuria is a screening tool for detection of CAA. In conclusion, although the majority of patients with CAA had sterile pyuria, this association is not statistically significant and it couldn't be considered as a predicting factor for CAA.

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