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Risk Factors of Coronary Involvement in Kawasaki Disease in Recent Outbreak in South Iran, Shiraz

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Abstract:

Background: During the past year, Kawasaki disease (KD) had an outbreak with a high incidence of coronary involvement in Shiraz, Iran. This study focuses on risk factors and their correlation with aneurysm formation.

Methods: All patients who were admitted with the diagnosis of KD in the pediatric units of Shiraz, Iran between 2009 and 2010 were included in this study. Data analysis was performed on demographic as well as clinical features, laboratory data, echocardiography, and electrocardiogram as well as treatment details.

Results: The population under study included 45 patients, 25 males (55.6%) and 20 females (44.4%), with the mean age of 3.52 ± 2.77 years. Aneurysm was seen in 10 cases (22.2%) with the male to female ratio of 9:1. The most important risk factor of aneurysm formation was the male gender with the odds ratio of 10.6. Age more than 8 years was a very specific but non-sensitive predictor of aneurysm formation (sensitivity: 40% and specificity: 100%). Platelet counts more than 424×10^3 was the most sensitive predictor of aneurysm formation (sensitivity: 90% and specificity: 57.1%). Fever duration more than 10 days had the sensitivity of 60% and the specificity of 88.6% for developing coronary aneurysm. No significant difference was seen in other clinical symptoms and laboratory data including complete blood count, liver function test, renal function test, electrolyte, and ECG data.

Conclusion: Male gender, older age, prolong fever before treatment, and higher platelet counts were the risk factors of coronary aneurysm in KD. More education for early diagnosis of Kawasaki disease in older patients is highly recommended.

Keywords Kawasaki, Aneurysm, Coronary Artery, Risk Factor, Delayed diagnosis

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Introduction

Kawasaki disease (KD) – which is known as mucocutaneous lymph node syndrome – is a self limited acute vasculitis syndrome which involves mainly small and medium size arteries and about 85% of its cases occur in children under 5 years old [1, 2].

KD is a leading cause of the acquired pediatric heart disease in developed countries. The most serious complication of KD is the development of coronary artery aneurysm which may cause mortality and morbidity [3]. Up to 25% of untreated children with KD develop

coronary artery aneurysm which reduced to less than 5% with early diagnosis and treatment [4]. The etiology of KD is still unknown but clinical and epidemiologic features of KD support an infectious cause [5].

The most important manifestation of KD is cardiac involvement. Two-dimensional echocardiography should be obtained as the baseline study, since the presence of KD is suspected. This is the choice study for evaluating the coronary artery aneurysm. The follow up echocardiography should be repeated after 2-3 weeks of illness. If both are normal, it should be repeated 6-8 weeks

after the onset of the disease. If echocardiography shows cardiac involvement at any time, frequent echocardiographical studies may be necessary. Treatment with intravenous immunoglobulin in the first 10 days of the disease reduces the incidence of the coronary artery aneurysm (CAA). The prognosis of patients with the CAA is poor when the aneurysms are giant (internal diameter >8mm) [6, 7, 8].

KD is common in Iran with high rate of aneurysm formation[9]. Moreover, KD had a high incidence of coronary involvement in the past year outbreak in Shiraz [1]. The present study, therefore, aims to evaluate the risk factors of the aneurysm formation in this disease.

Materials and Methods

This retrospective study was performed on all children who were admitted in the pediatric unit of Namazi and Dastgheib hospitals (the main referral centers of pediatric in Shiraz, Iran) with the diagnosis of KD between 2009 and 2010.

Diagnosis of KD was based on the presence of fever and three or four of the classic criteria associated with the coronary Aneurysms (Table1) [5].

Table1 - Diagnostic criteria for classic KD

Fever of at least 5days duration
Plus 4 of 5 following feature:
- Bilateral nonexudative bulbar conjunctival injection
- Polymorphous exanthema
- Cervical lymphadenopathy >1.5 cm usually unilateral
- Changes in lip and oral cavity (erythema, lip cracking, strawberry tongue)
- Changes in extremities: erythema of palm and sole , edema of hands , feet and desquamation
- Exclusion of other disease

Demographic and clinical features, laboratory data, imaging findings including echocardiography, electrocardiogram and chest radiography, and treatment details as well as the follow up were gathered from patients' profiles. Also, standard questionnaires were completed according to these items. Two-dimensional echocardiography was done for all the patients at the time of diagnosis by the pediatric cardiologist. The coronary

aneurysm was considered to exist when the internal luminal diameter was either over 3 mm in children below 5 years old, or over 4 mm in 5 or more years old children. Statistical analysis was performed by the SPSS statistical software. In addition, Chi-square, Fisher's exact tests, independent sample *t*-test, and receiver operating curve (ROC) were used for the comparison between the groups and the determination of the sensitivity as well as the specificity. Also, the *p* value <0.05 was considered as statistically significant.

Results

The population under study included 45 patients with the final diagnosis of KD who were admitted in the pediatric units of Namazi and Dastgheib hospitals (Shiraz, Iran) during the study period. 10 (22.2%) patients had the coronary aneurysm, while 35 (77.8%) had no coronary involvement according to our definition.

In our study, we compared the recorded demographic, clinical, and laboratory findings in aneurysmal and non-aneurysmal group. The results are summarized in Table 2.

The most common symptoms and signs were conjunctivitis in 36 cases (80%) and mucosal changes in 33 ones (73%) (Table2). There were 25 males (55.6%) and 20 females (44.4%) (Male to female ratio= 1.25:1). From 10 patients who had the coronary involvement, 9 (90%) were males and 1(10%) were females, which was significantly different from the patients without the coronary involvement (*p*= 0.03). The most important risk factor of the aneurysm formation was sex with the odds ratio of 10.6 for male to female (Table 3).

The mean age of the patients was 3.52±2.77 years. The mean age of the aneurysmal group and the non-aneurysmal group was 5.27±4.48 and 3.02±1.87, respectively (Table 2). The mean age was significantly different between the two groups (*p*= 0.022). Age more than 8 years had the sensitivity of 40% and the specificity of 100% for detecting the coronary aneurysm in our study (Fig 1).

The mean duration of fever at the diagnosis in the aneurysmal and the non-aneurysmal groups was 11.90±4.95 and 7.86±5.28 days, respectively. There was a statistically significant difference between the two group regarding fever duration (*P* = 0.036).

Fever duration more than 10 days had the sensitivity of 60% and the specificity of 88.6% for developing the coronary aneurysm (Fig 2).

Table 2- Demographic, clinical and laboratory findings of patients with and without aneurysm

Variables	Aneurysmal group		Non Aneurysmal group		Total		P value
	Number	Mean	Number	Mean	Number	Mean	
Age(years)		5.27± 4.48		3.02± 1.87		3.52± 2.77	P = 0.022
Under 5 yr	6(60%)		29 (82.8%)				
Higher than 5 yr	4(40%)		6 (17.2%)				
Sex							
Male	9 (90%)		16 (45.71%)		25 (55%)		P = 0.03
Female	1 (10%)		19 (54.29%)		20 (45%)		
Fever duration days		11.90± 4.95		7.86± 5.28		8.76± 5.43	P = 0.036
WBC count		13440± 9296		13754± 6178		13684± 6869	NS*
Platelet count		643000 ± 223082		432514±152991		479288± 189994	P = 0.027
Hemoglobin		10.2±1.5		10.7±1.5		10.6±1.5	NS
ESR (mean)		75±25.3		68±24.2		69.5±24.3	NS
AST (mean)		34.3 ±25.3		39.5± 23.8		38.1± 24	NS
ALT (mean)		47.40 ±72.5		47.4± 72.5		42.4± 67.9	NS
Hospitalization days		15.2 ±11.8		5.1±1.8		7.1±6.7	P = 0.03
Fever duration after treatment (Hours)		82.6 ±63.6		44.2 ±24.9		52.9 ±39.6	P = 0.009
Rash	5 (50%)		26 (74.3%)		31 (68.9%)		NS
Pilling	3 (30%)		12 (34.3%)		15 (33.3%)		NS
Mucosal Change	8 (80%)		25 (71.4%)		33 (73.3%)		NS
LAP	4 (40%)		17 (48.6%)		21 (46.7%)		NS
Tachycardia	9 (90%)		22 (62.9%)		31 (68.9%)		NS
Extremity edema	4 (40%)		11 (31.4%)		15 (33.3%)		NS
Conjunctivitis	8 (80%)		28 (80.0%)		36 (80%)		NS
Arthritis	0 (0 %)		5 (14.3%)		5 (11.1 %)		NS
Pyuria	3 (30%)		11 (31.4%)		14 (31.1%)		NS

*NS: Not significant p value (P value > 0.05)

Table 3- Odds ratio and 95%confidence interval of risk factors for the coronary aneurysm

Variables	Odds Ratio	95%Confidence Interval		P Value
		Lower	Upper	
Sex (M/F)	10.688	1.220	93.640	p<0.05
Fever duration before Treatment >10 days	5.091	1.103	23.493	p<0.05
Age ≥ 5 years old	3.222	.690	15.039	p<0.05
Thrombocytosis (Plt ≥ 424×103)	10.688	1.220	93.640	p<0.05
Fever duration after treatment >48 h	7.350	1.287	41.984	p<0.05



Fig 1: Sensitivity, specificity, and cut-off point for age in patients with and without coronary aneurysm

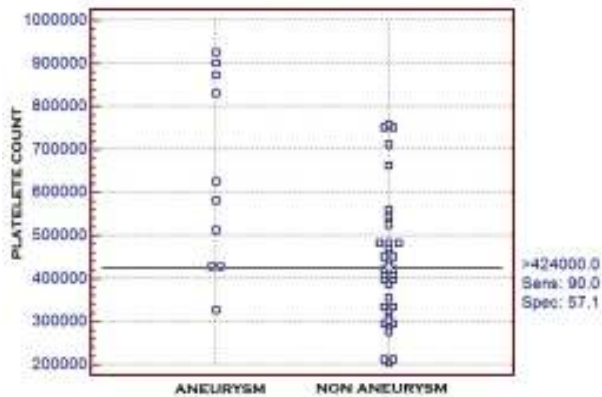


Fig2: Sensitivity, specificity, and cut-off point for fever duration before starting the treatment in patients with and without coronary aneurysm

The mean duration of the disappearing fever after starting the treatment with immunoglobulin was 89.90 ± 39.66 hours (82.67 ± 63.62 hours in the aneurysmal group and 44.26 ± 24.96 hours in the non-aneurysmal group). Regarding the duration of the disappearing fever, a statistically significant difference was found between the two groups ($p = 0.009$).

Duration of the disappearing fever more than 48 hours after the treatment with intravenous immunoglobulin had the sensitivity of 77.8% and the specificity of 67.7% for developing the coronary aneurysm.

The mean platelet count was 643000 ± 223082 cells per mm^3 and 432514 ± 152991 cells per mm^3 in the aneurysmal group and the non-aneurysmal group, respectively. The platelet count was found to be significantly different between the two groups ($p = 0.027$). The platelet count more than 424×10^3 cells per mm^3 had the sensitivity of

90% and the specificity of 57.1% for developing the coronary aneurysm (Fig 3).

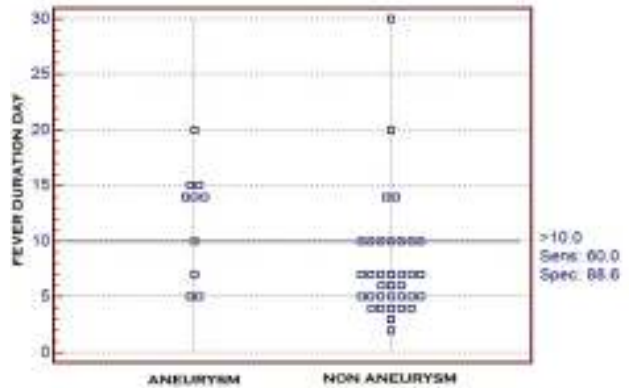


Fig 3: Sensitivity, specificity and cut-off point for platelet count in patients with and without coronary aneurysm.

The analysis showed that the odds ratio for developing the coronary aneurysm among Kawasaki patients with the platelet count more than 424×10^3 cell per mm^3 was 10.5.

The mean hospitalization days among the aneurysmal and the non-aneurysmal groups were 15.22 ± 11.8 and 5.11 ± 1.8 days, respectively ($p = 0.03$).

There were no significant differences in the patients' characteristics including conjunctivitis, arthritis, extremity edema, tachycardia, pilling, mucosal change, and lymphadenopathy in both groups ($p > 0.05$).

Discussion

Cardiac involvement is the main cause of the long term morbidity and mortality in KD [5]. In a study which was conducted by Asadi-pooya et al. in Shiraz, Iran, from 113 Kawasaki patients, 10 had the coronary involvement during 12 years [1]. In our study, however, during one year, from 45 patients, 10 had the aneurysm. Therefore, the incidence of the aneurysm has significantly increased and evaluation of the risk factors for the aneurysm is critical.

The distribution of age and sex among patients in our study is similar to most of the previous studies [10, 11].

Male gender with the odds ratio 10.6 is the major risk factor of the coronary aneurysm (Table 3). This result is compatible with other studies which showed a higher incidence in the male gender [8, 12].

Older age had a higher risk of the coronary aneurysm and age more than 8 years old could predict the aneurysm formation with 100% specificity. On the other hand, all children over 8 years old are at risk of the aneurysm formation. Similar results were reported by other authors,

as well [13]. KD is a common disease at age below five years old [14]. Therefore, delay in the diagnosis and treatment of older patients may lead them to the aneurysm formation.

Data analysis revealed that longer fever duration was another risk factor of the coronary aneurysm. This finding is similar to studies performed by Davaalkham et al., Asai et al., and Asadi-pooya et al. [1, 8, 15].

An interesting result was found regarding the fever duration; before the treatment, fever more than 10 days had the odds ratio of 5.09, and fever duration more than 14 days increased the odds ratio of the coronary aneurysm formation up to 11.6 (Table 3). It proves the role of the delayed diagnosis in the aneurysm formation; therefore, the increasing index of suspicion for the early diagnosis and treatment of KD had an important role in reducing the coronary aneurysm.

Prolonged fever duration after the treatment with intravenous immunoglobulin, also, increases the risk of the aneurysm. After the treatment, duration of fever more than 48 hours was a risk for developing the coronary aneurysm with the odds ratio of 7.35 (Table 3). This is similar to the study conducted by Tae Yeun Kim [16].

Thrombocytosis was another predictive risk factor for developing the aneurysm. About 90% of Kawasaki patients with the coronary aneurysm had the platelet count $\geq 424 \times 10^3$ cells per mm^3 with the odds ratio of 10.6 (Table 3). It is similar to the study by Asadi-pooya [1]; however, Honkanen reported no relationship between thrombocytosis and aneurysm [17].

Since the majority of the aneurysmal patients had thrombocytosis, it may be due to the late diagnosis of KD which was accompanied by thrombocytosis.

Prolonged hospitalization stay was another risk factor for the aneurysm. It may be related to the poor response to the treatment or the prolonged fever after the treatment.

Several studies have been done on the risk factors for the coronary involvement in KD. In his study, Asai showed that the risk factor for developing the aneurysm in KD included age <1 years, male gender, fever duration more than 14 days, $\text{ESR} > 101$, elevated $\text{ESR} > 30$ days, hemoglobin < 10 , and leukocyte count > 30000 [8].

Asadi-pooya et al., reported that the prolonged fever as well as thrombocytosis were risk factors for coronary artery abnormalities [1].

In this study, there were no significant differences in other variables including complete blood count, liver function test, renal function test, electrolyte, and electrocardiogram data in both groups.

Among our findings, early diagnosis of KD before 10 days and attention to KD in older patients were two preventable variables. Education of physicians for the early detection of KD can also decrease the complication of this disease.

Conclusion

Male gender, older age, delayed diagnosis, and thrombocytosis were the risk factors of the coronary aneurysm in KD. So, more education for the early diagnosis and treatment of KD is highly recommended.

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