Epidemiological Features and Clinical Study of Kawasaki Disease in Iran

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Abstract- Kawasaki disease (KD) is an acute febrile systemic vasculitis of unknown etiology and the major cause of pediatric acquired cardiac disease worldwide, particularly in developed countries. This study characterizes the epidemiologic and clinical features of KD in the Pediatric Rheumatology Department service in a general hospital. 120 patients with the diagnosis of KD between 1990 and 2009 were enrolled. We investigated the epidemiologic and clinical features of coronary artery involvement of the patients. Frequency of many parameters including age, sex, season, clinical and laboratory findings, response to treatment, and complications of the patients determined. During the 20-year study period, 120 patients <15 years of age were admitted for KD. Among them, 39.2% were at the extremes of the age spectrum, with 2.5% <6 months and 36.7% >5 years of age, male to female ratio of 1.3:1 and the classic KD to incomplete KD ratio of 3.1:1. KD recurred in 5% of all cases. It occurred most frequently in the winter and least frequently in the summer. The occurrence of coronary artery abnormalities (CAA) was 4.2%. Kawasaki disease should be considered in any pediatric patients with a prolonged refractory febrile illness in order to prevent CAA formation.

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Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis of unknown etiology with multiple organ involvement that occurs predominantly in children younger than 5-year-old (1). About 80% of the patients are between 1 and 5 years of age (2,3), with a male-to-female ratio of 1.5:1 (1).

Since the introduction of KD, it is considered the major cause of pediatric acquired cardiac disease worldwide, particularly in developed countries (3). Infections can trigger the immune response in genetically susceptible individuals, which may lead to KD (4).

The diagnosis made by clinical criteria, including fever lasting more than 5 days with conjunctival and oral mucosa changes, fissured lips, cervical lymphadenopathy, skin rash, and palm/sole erythema/edema (3). Laboratory findings associated with KD, such as anemia, thrombocytosis, leukocytosis, elevated erythrocyte sedimentation rate (ESR), and positive C-reactive protein (CRP), can support the diagnosis. Coronary artery aneurysms are seen in 20-40% of untreated patients leads to long-term sequels, including coronary stenosis, early atherosclerosis, and myocardial infarction (5). Treatment with intravenous immune globulin (IVIG) and aspirin can reduce the risk of coronary artery disease (CAD) by ten-folds (6,7) as long as their beneficial effects on other complications such as carditis, arthritis, hepatitis, central nervous system (CNS) involvements (1), kidney and urinary tract abnormalities (8) and muscle involvement (9).

The term atypical or incomplete Kawasaki disease describes patients who have CAD but not strictly meeting the diagnostic criteria of KD (10,11).

According to epidemiologic studies, the incidence of KD is high among the Asian population. It is also a common rheumatologic disease in Iran. Accordingly, we decided to perform this study to describe the demographics and clinical features of KD at the pediatric Rheumatology department in Imam Khomeini general hospital in Tehran.

Material and Methods

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The medical records of all children with the KD diagnosis who have been admitted to the pediatric rheumatology department of Imam Khomeini general hospital between 1990 and 2009 were reviewed.

Patients' Demographics and characteristics of the disease were abstracted, including age, sex, family history, recurrence, season, clinical and laboratory findings, coronary artery involvements, and other organs' involvements. The diagnosis was based on the criteria of the Japan Kawasaki Disease Research Committee (12,13). Patients with persistent fever with fewer than four other features of the disease were described as atypical or incomplete KD (7).

Echocardiographic evaluation was performed for all patients for cardiac complications assessment. Coronary artery abnormality (CAA) attributed to KD was defined based on the Japanese Ministry of Health Criteria: (1) coronary artery branch internal lumen diameter ≥3 mm for children <5-year-old and ≥4 mm for children ≥5-year-old; (2) internal diameter of a segment at least 1.5 times as large as that of an adjacent segment, and (3) a clearly irregular lumen (14).

The research ethics board of Tehran University of Medical Sciences approved the study and waived the requirement for informed consent for this retrospective study.

Statistical analysis

The data were reported as mean±standard deviation or percentage. Nominal data and continuous data were analyzed using the X^2 test and the unpaired *t*-test, respectively. A $P<0.05$ was considered to be statistically significant. Data were analyzed using SPSS for Windows, version 17.

Results

One hundred and twenty patients with a diagnosis of KD (classic and incomplete) during the 20-year period between 1990 and 2009 were enrolled in our study. The mean age of the patients was 50.7±34.2 months with a range of 3 months to 15 years. Among all patients, 39.2% (47 cases) were at the extremes of the age spectrum, with 2.5% (3 cases) under 6 months and 36.7% (44 cases) over 5 years of age.

Sixty nine patients (57.5%) were male, with a male/female ratio of 1.3:1. Ninety one patients (75.8%) met all 5 criteria of KD (classic KD), and 29 (24.2%) met less than 5 criteria (incomplete KD), with the classic KD/incomplete KD ratio of 3.1:1. The interval between fever onset and diagnosis was 14.46±11.54 days. There was no family history of KD in first-degree relatives.

Most of the patients were admitted in winter (30.8%) and spring (29.2%), and the remaining cases in the autumn and summer (25.8% and 14.2%, respectively). IVIG was administered for all patients, of which 115 patients (98.5%) were free of fever within 48 hours after IVIG administration, while the other 5 patients needed a second dose of IVIG.

Table 1 compared the clinical characteristics of the patients related to the KD diagnostic criteria at diagnosis in different age groups. Fever was present in all patients. The most presented clinical findings along with fever were skin rash (66.6%), bilateral conjunctivitis (65.0%), and mucosal erythema (63.3%), respectively.

The laboratory values of the patients at diagnosis are summarized in Table 2.

Table 1. Clinical characteristics of patients at diagnosis

		< 6mo (3)	6mo – 5y (70)	> 5y (47)	Total (120)
	Fever	3 (100%)	70 (100%)	47 (36.7%)	120 (100%)
Findings	**Skin rash**	3 (100%)	45 (64.3%)	32 (68.1%)	80 (66.6%)
	Cervical lymphadenopathy	0 (0%)	23 (32.9%)	14 (29.8%)	37 (30.9%)
	Erythema/Edema	0 (0%)	28 (40.0%)	14 (29.8%)	42 (35.0%)
Changes in extremities	**Scaling**	1 (33.3%)	29 (41.4%)	33 (70.2%)	63 (52.5%)
	Bilateral conjunctivitis	2 (66.7%)	48 (68.8%)	28 (59.6%)	78 (65.0%)
Changes in the oral cavity and lips	**Mucosal erythema**	0 (0%)	48 (40.0%)	28 (59.6%)	76 (63.3%)
	Fissured lips	2 (66.7%)	37 (52.9%)	24 (51.1%)	63 (52.5%)
	Strawberry tongue	1 (33.3%)	40 (57.1%)	26 (55.3%)	67 (55.8%)

Values given as number (percentage); mo= months; y= Years

Table 2. Laboratory values of patients at diagnosis

Hb (g/dl)	11.7 ± 1.6 (8.4 – 17.1) *
< 9	13 (10.8%) **
9-11	25 (20.8%)
> 11	82 (68.4%)
WBC (/mm^3)	11997 ± 4941 (3400 – 30500)
< 10000	45 (37.5%)
10000-15000	45 (37.5%)
> 15000	30 (25.0%)
Platelet (/mm^3)	407613 ± 226838 (53000 – 1267000)
< 150000	5 (4.2%)
150000-450000	70 (58.3%)
450000-750000	39 (32.5%)
> 750000	6 (5.0%)
ESR (mm/h)	48.4 ± 32.5 (5 – 123)
< 15	19 (15.8%)
15-30	20 (16.6%)
31-50	29 (24.2%)
51-80	28 (23.4%)
81-100	13(10.8%)
> 100	11 (9.2%)
CRP (mg/dl)	39.5 ± 26.6 (1.5 – 87)
AST (Iu/l)	58.2 ± 143.1 (14 – 925)
ALT (Iu/l)	65.6 ± 251.08 (8 – 1625)
ALP (Iu/l)	398.5 ± 136.3 (139 – 775)
Sodium (mm/l)	139.1 ± 3.7 (130 – 145)
Potassium (mmol/l)	4.3 ± 0.6 (2.8 – 7.3)

*Values given as Mean ± SD (Range); **Values given as number (percentage); ALP= alkaline phosphatase; ALT= alanine aminotransferase; AST= aspartate aminotransferase; CRP= C-reactive protein; ESR= erythrocyte sedimentation rate; Hb= hemoglobin; WBC= white blood cell count

Table 3. Other clinical findings of patients at diagnosis

Cardiovascular	**Myocarditis**	1 (0.8%)
	Pericarditis	1 (0.8%)
	Mitral valve regurgitation	15 (12.5%)
	Coronary artery abnormalities	5 (4.2%)
	Raynaud phenomenon	2 (1.7%)
	Peripheral gangrene	1 (0.8%)
Musculoskeletal system	**Arthritis**	2 (1.7%)
	Arthralgia / Myalgia	27 (22.5%)
Gastrointestinal tract	**Vomiting/ nausea / abdominal pain**	66 (55.0%)
	Anorexia	32 (26.7%)
	Hydrops of gallbladder	1 (0.8%)
Central nervous system	**Irritability**	24 (20.0%)
	Sensorineural hearing loss	1 (0.8%)
	Aseptic meningitis	1 (0.8%)
Genitourinary system	**Meatitis**	3 (2.5%)
Skin	**Beau's line**	1 (0.8%)
	Perineal desquamation	24 (20.0%)
	Desquamating rash in the groin	9 (7.5%)

Values are given as a number (percentage)

Other clinical findings are summarized in Table 3. The most cardiovascular complication was mitral valve regurgitation, presented in 15 patients (12.5%). No valvular stenosis, congestive heart failure, or vascular thrombosis was detected among patients. The mean age of patients with cardiovascular complications was

significantly higher than patients without cardiovascular complications (72.3±51.5 months vs. 47.9±32.0 months; *P*=0.032). CAA was reported in 5 patients (4.2%); all of them were males. Based on echocardiography of the patients with CAA, 4 had a coronary aneurysm (3.3%), and one patient had coronary ectasia (0.8%). Patients with CAA had a significantly longer duration of fever prior to hospitalization than the ones without CAA (13.68±11.05 days vs. 23±13.96 days; *P*=0.01).

There was no mortality among our study population.

Discussion

Kawasaki disease is an acute febrile vasculitis of unknown origin (2). The epidemiology of KD in Iran is not well described. Kawasaki disease is more common in boys than girls (15), and 85% of cases occur in children <5-year-old (16). A study from the United States also showed that KD is more common during the winter and that 76% of children are <5-year-old (17). In another study from China, 82.3% of patients were <5-year-old (18). Studies revealed the highest seasonal incidence of KD in the summer (Taiwan and Korea), in the spring and summer (Beijing and Hong Kong), in January and summer (Japan) (19-23). Studies from Europe and Canada report the highest incidence in the winter months (11,24).

Like other studies, we found a higher incidence of KD in males (male: female ratio of 1.3:1), during certain seasons (winter and spring), and in children <5-year-old between 1990 and 2009. In a study from Canada, 4% of KD patients were <6 months of age at diagnosis, and 25% of them were >5-year-old (25). In our study, 2.5% and 36.7% of patients were <6 months of age and >5 years of age, respectively.

Kawasaki disease is mainly a clinical diagnosis, and there are no pathognomonic laboratory tests or findings (26). The diagnosis is confirmed by meeting certain criteria. Fever is a mandatory criterion of KD diagnosis (12,13). In our study, in addition to fever, skin rash was the most commonly detected clinical sign, as found in other studies from Iran and other countries (27-29). Cervical lymphadenopathy was the least common of the principal clinical features (30.9%).

Leukocytosis is a typical feature of the acute phase of KD. Approximately 50% of patients had white blood cell (WBC) counts> 15,000/mm³ (26).In contrast to other reports (26,30), the mean leukocyte count of our study group was 11,997±4,941, and only 25% of patients had a WBC count of >15,000. Given that in our study group, the interval between fever onset and diagnosis of KD in referred patients to our clinic, leukocyte count was being fallen in this prolonged period.

In KD, anemia may occur (26). The mean hemoglobin value of our study patients was 11.7±1.6 g/dl with marked anemia (Hb<11) in 31.6% of patients. In a Turkish study (26), anemia was observed in 40% of patients.

Thrombocytosis is a characteristic feature of the subacute phase of KD, appearing in the second week and peaking in the third week with a gradual return to normal by 4-8 weeks of onset in uncomplicated cases. Platelet counts are usually >450,000/ mm³ in patients diagnosed within seven days of onset (26). In our study, most patients were referred and diagnosed between days 7 and 10 after illness onset, and the mean platelet count was 407,613±226,838/ mm³ with >450,000/ mm³ in 37.5% of cases. In the Turkish study (26), most of the patients were diagnosed in the second week, and the mean platelet count was higher compared to our study (490,889±208,503/ mm³ vs. 407,613±226,838/ mm³). This difference may be due to the early diagnosis of KD (days 7-10) in our study compared with their study.

Elevated ESR is a typical laboratory finding in KD, usually returning to normal values by 6-8 weeks after illness onset (26,31). Similar to other studies (26,28,29), the mean value of ESR was high in our cases, with 48.4±32.5 mm/h. Moreover, ESR > 100 was observed in 20% of cases.

Other organs involvement may be observed in KD (26,31). Gastrointestinal complaints, including diarrhea, vomiting, nausea, anorexia, abdominal pain, and hydrops of the gallbladder, occur in about one-third of the patients (32). In contrast to other studies (26), the most prevalent complaints of our patients at diagnosis were gastrointestinal (82.4%). Other prevalent clinical findings included irritability (20%), perineal desquamation (20%), and arthralgia and myalgia (22.5%).

Peripheral ischemia with resultant gangrene is a rare but serious complication of KD (33). Patients with this complication have been reported previously (33,34). In our study, peripheral gangrene was observed in one case. Also, the Reynaud phenomenon was observed in the mentioned patient and another case.

KD should be considered in any infant or child (especially less than two years old) with a prolonged refractory febrile illness.

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