Iranian Journal of Pediatrics Society
Volume 1, Number 1, 2007: 41-46

Original Article

Kawasaki Disease in 159 Iranian Children

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ABSTRACT

***Background**: The diagnosis of Kawasaki Disease (KD) is made by clinical criteria. Intravenous immunoglubolin is dramatically effective in this disease. The aim of this study was to describe the initial diagnosis of Kawasaki disease in Iranian children. We describe the clinical manifestation, organ involvement, management, rate of cardiac anomaly and treatment of Kawasaki disease in Iran.*

***Materials and Methods**: This prospective multicenter study enrolled 159 children with Kawasaki disease. Medical records of all cases of KD treated at pediatric rheumatology department of Children's Hospital between January 1994 and July 2004 were reviewed.*

***Results**: One-hundred fifty-nine patients were identified. Demographic features were similar to those reported by other countries. One hundred twenty-five children fulfilled the criteria for typical KD while thirty-four cases had atypical KD.*

Echocardiographic abnormalities were found in 30 cases, including 20 with coronary arteries aneurysms, and 10 with other abnormalities, but abnormalities were eventually resolved in 15 cases, and remained in 5 cases.

***Conclusion**: Kawasaki disease is a pediatric febrile systemic vasculitis, affecting any organ; although it seems to have a predilection for coronary vessels.*

It is important to consider KD in any children with unexplained fever. Careful initial evaluation, treatment in the acute phase, and long-term management of patients with coronary artery involvement are recommended.

***Keywords:** Kawasaki disease, Syndrome, Children*

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INTRODUCTION

Kawasaki disease is a multisystemic generalized medium and small vessels vasculitis of unknown etiology (1), which predominantly affects children under the age of 5 years. It is also one of the most common causes of acquired heart disease among children living in developed countries.

The disease was first described in 1967 by Kawasaki, based on findings in 50 Japanese children (2). Kawasaki described a unique illness characterized by fever, changes in the oropharynx such as fissured lips and strawberry tongue, bilateral conjunctival injection without exudate, cervical lymphadenitis, polymorphic exanthema rash, redness

and swelling of the hands and feet and erythema of the palms and soles (3,4,5). In the early 1970s Melish et al. reported 12 children from Honolulu with the same illness pattern. Kawasaki disease has now been reported worldwide (6).

In the presence of classic features, many experts believe that the diagnosis of KD can be made with fewer than 5 days of fever, and fewer than 4 principle symptoms (4,5). Anemia, thrombocytosis, leukocytosis, elevated erythrocyte sedimentation rate (ESR), positive C-reactive protein (CRP), and other laboratory tests are associated with KD and can support the diagnosis. Coronary artery aneurysm, the most serious consequence of KD, is seen in 20% to 25% of untreated patients. Long-term consequences include coronary stenosis, early atherosclerosis, and myocardial infarction (7).

In atypical or incomplete KD, the patients do not strictly meet the diagnostic criteria but have coronary artery changes (9,10,11,12).

We describe the demographic and clinical features of KD at Pediatrics Rheumatology Department of Children's Hospital (the largest pediatric referral center in Iran). Cases were analyzed with respect to the fulfillment of diagnostic criteria, the presence of surrogate markers, echocardiographic findings, and treatment decisions.

Fortunately, the risk of coronary artery abnormalities decreases by ten fold in patients treated with intravenous immunoglobulin (IVIG) and aspirin (13, 14, 15, 16).

MATERIALS AND METHODS

One hundred fifty-nine children diagnosed as having KD in the pediatric rheumatologic department of Children's Hospital, Tehran University of Medical Sciences between January 1994 and July 2004 were included in the study. Hospital records and/ or rheumatologic clinic charts were reviewed, and data were abstracted onto standardized forms. All cases were established according to the study group's diagnostic guidelines for KD based on the criteria of the "Japan Kawasaki Disease Research Committee".

The questions included age at onset of disease, sex, clinical data, presence and duration of fever, other diagnostic criteria, laboratory tests (lowest hemoglobin, highest platelet count, highest pretreatment ESR, and positive CRP), echocardiography feature, outcome, details of treatment and follow-up.

Definition of the inclusion and exclusion criteria:

There were 159 patients who met the inclusion criteria. All cases included in the study were younger than 6 years of age, had fever for five or more days, and had 4 of the 5 following clinical criteria at the onset of disease (12):

1- Changes in the oropharynx
2- Bilateral conjunctival injection
3- Cervical lymphadenitis
4- Polymorphic exanthema rash
5- Redness and swelling of the hands and feet and erythema of the palms and soles.

Patients with atypical or incomplete KD have been described as not strictly meeting the diagnostic criteria but have coronary artery changes. Aneurysm, dilatation, or ectasia of coronary arteries were also seen in echocardiography (8,9).

RESULTS

One hundred and fifty-nine patients were diagnosed as having KD during a 10-year period. Patients' age ranged from 3 months to 6 years, with a median of 2.8 years. Seventy-five percent (120 cases) of patients were under the age of 5 years, with 15% (23 cases) being under 1 year old at the time of diagnosis, and 10% (16 cases) being older than 5 years old (Table 1). Eighty-seven (54%) patients were males and 72 (45%) were females. Male to female ratio was 1.2:1 (Table 2). Eighty patients (50%) fulfilled 5 of the clinical criteria for KD, 52

cases (32%) fulfilled 4 criteria, 20 cases (12%) fulfilled 3 criteria, and 7 patients (4%) fulfilled 2 criteria, (Table 3).

Table 1. Age at onset in 159 patients with KD.

Age/Y	No	Percent
<1/y	24	15
1-2/y	42	26
2-3/y	51	32
3-4/y	22	14
4-5/y	11	7
5-6/y	6	4
>6/y	3	2

Table 2. Sex distribution in 159 patients with KD

Sex	No	Percent
Male	87	55
Female	72	45
Ratio	1.2:1	1.2

Table 3. Clinical features at onset in159 patients with KD

Clinical features	No	Percent
Fever<5 days	76	47
Fever >5 days	83	52
Changes in oral cavity and lips	149	93
Bilateral conjunctiva injection	128	80
Changes in extremities	100	62
Polymorphic exanthema	98	61
Cervical lymphadenopathy	95	59
Number of criteria meet KD=5	80	50
Number of criteria meet KD=4	53	33
Number of criteria meet KD=3	21	13
Number of criteria meet KD=2	2	1.2

Clinical Manifestations

Seventy percent of these cases were diagnosed within the first 10 days, with the longest time of diagnosis being 25 days. Oral changes such as dry cracked lips, fissured lips, strawberry tongue, and pharyngeal inflammation were seen in 139 (87%) cases. Bilateral conjuctival injection without exudates was seen in 130 (82%) cases. Cervical lymphnode enlargement was reported in 20 (75%) patients. Rashes were mainly maculopapular or polymorphic exanthema which were seen in 115 (72%) cases. Extremity changes included redness and swelling, erythema and desquamation of the palms and soles which were seen in 115 (72%) cases (Table 4).

Table 4. Other organ involvements in 159 patients with KD

Organ involvement	No	Percent
Persistent fever> 10 days	75	47
Irritability	127	79
Desquamation of finger tips	97	61
Coronary aneurysms, and ectsia	60	38
Respiratory tract, cough, coryza	45	28
Erythema & induration at BCG inoculation site	23	14
Gastrointestinal: vomiting, diarrhea,	23	14
Gallbladder hydrops	14	8
Abnormal liver function test	16	10
Genitourinary system: urthritis& meatitis	40	25
Sterile pyuria	38	23
Anterior uveitis	15	9
Arthralgia	35	22
Arthritis	25	15
Convulsion	12	7
Aseptic meningitis	12	7
CSF pleocytosis	15	9
Facial palsy	1	0.06
Beau's line	25	15

Laboratory findings:

Anemia with hemoglobin< 10.5 mg/dL was seen in 147 (92%) cases. Leukocytosis (WBC count 15.000-30.000) was seen in 129 (81%) cases. Thrombocytosis (platelet count 300.000>500.000/mm^3) was seen in 96(60%) patients. CRP was positive (+++), and erythrocyte sedimentation rates were 55>105-/mm/hour in 150 (94%) cases. Abnormal liver function test was reported in 20 cases (Table 5).

Table 5. Laboratory findings in 159 cases with KD.

Lab test	No	Percent
Lab<9 gr/dl	145	91
Leukocyte count> 30.000	150	94
Platelet count >500.000	127	79
Platelet count >700.000	104	65
ESR> 50	152	95
ESR>70-100	142	98
C-reactive-protein> +++	145	91
Abnormal-LFT	45	28
Hypoalbuminemia	25	15
Leukocyte Synovial fluid	12	7
Sterile pyuria	22	13
Pleocytosis in CSF	12	7
Positive blood culture	0	0
Positive urine culture	0	0
Positive throat culture	0	0

On abdominal ultrasound, hydrops of the gall bladder was reported in 39 patients.

"Color Doppler Echocardiograms" were obtained at the time of diagnosis, 14 to 21 days, 60 days, and 1 year after the treatment. Coronary or other arterial abnormalities were reported in 30 (18.8%) patients, 21 males and 9 females, (2 cases, a 3-month girl infant and a boy aged 5 years, developed giant aneurysms, lumen diameter >8mm).

Echocardiographic findings, were present in 12 patients who had fever plus 5 diagnostic criteria, in 10 cases who had fever plus 4 criteria, and in 8 patients who had fever with 3 diagnostic criteria of KD.

Echocardiographic changes were as follows: 8 cases showed definitive aneurysms, 8 cases had ectasia, 6 cases had perivascular edema, 4 cases had pericardial effusions, 2 cases had mitral regurgitation and 2 cases had myocarditis.

All patients received one dose of IVIG 2g/kg single dose, and also received aspirin, with anti-inflammatory doses (100 mg/kg/day) for the first 2 weeks, followed by antiplatelet doses (3 to 5 mg/kg/ day) for the next 6 weeks.

Twenty-four children (15%) also received antibiotics during the course of their illness, and 15 patients were treated with methylprednisolone after two doses of IVIG.

DISCUSSION

KD is a generalized vasculitis of unknown etiology, which mainly affects young children. About 80% of patients are under 5 years old and usually between 1 and 5 years of age; the mean age is 2.5 years (1-2). Kawasaki disease is more common in males with a male-female ratio of 1.5:1. (3).

There is no specific test for the diagnosis of KD. The diagnosis is established by meeting certain criteria (4). According to the Japanese diagnostic guideline of KD, diagnosis is made based on the recognition of five or six main symptoms. If only four main symptoms are present, but echocardiography or angiography reveals coronary arterial changes, the Japanese diagnostic guideline recognizes the disease as KD (5,6).

We described 159 children who met the criteria for KD. This study disclosed the clinical pictures of KD. The demographic features closely parallel those reported from diverse regions of Iran.

In our case series, 125(79%) patients fulfilled the criteria for typical KD, and 34 cases (21%) fulfilled the criteria for atypical Kawasaki disease (5,6).

Typical Kawasaki disease has a well-characterized clinical course. In our series, all children with Kawasaki disease were generally irritable and uncomfortable (8, 9, 10).

Fever was usually high and spiking, exceeding 102ºF in almost all cases, compared with the previous report. In 129 cases conjunctival injection was seen more prominently as bulbar than palpebral without associated exudates (11). Oropharyngeal changes were seldom associated with red lips but strawberry tongue and pharyngeal redness were seen in 149 cases (93%). The rash seen in 98 (61%) cases was erythematous, and diffuse maculopapular.

Urticaria, scarletiniform rash rarely occurred in our series. Extremity changes were striking, with induration and erythema beginning abruptly at the

wrists or ankles in 100(62%) of our cases. Lymphadenophaty, usually unilateral, was seen in the course of disease and resolved at the fifth day of fever in 95 (59%) cases of our series (12, 13).

Subsequent periungual desquamation occurred in all cases 2 to 3 weeks after onset of fever.

Most clinical manifestations of our series were diagnosed in the 1st or 2nd week of illness. Cardiac abnormalities occurred in the 2nd - 4 th week of illness.

In our series approximately 30 cases (18%) developed cardiac problem, including coronary artery aneurysms (CAAs) in 8 cases, arterial ectasis in 8 cases, pericarditis with pericardial effusion in 6 cases, acute myocarditis, congestive heart failure (CHF) in 2 cases, and mitral insufficiency in 4 cases (7, 8, 9).

Aneurysms developed in only 2 cases who had been treated with intravenous gamma globulin before the 10th day of illness, facial nerve palsy occurred in one girl<2 years old with active KD, and resolved 1 to 2 weeks after treatment with IVIG (14,15).

Kawasaki disease has many other manifestations that reflect its systemic nature. Arthritis persists in 10% to 15% of our series, and often involves small joints of the fingers and toes. Arthritis appears to be more common in girls than in boys (8,11,12).

Urethritis with sterile pyuria were present in 30% of cases. Mild hepatitis with 2 to 4-fold elevation of transaminase occurred in 20% of cases. Diarrhea, nausea or vomiting may be present, usually due to hepatic inflammation. Hydrops of the gallbladder occurs in<8% of cases and may cause severe right upper quadrant pain.

Intravenous immunoglobulin with aspirin dramatically changed the management of KD. Treatment is more effective if started within 10 days of onset of fever (16, 17, 18). If a child clearly meets the criteria for KD, the decision regarding treatment with IVIG is not difficult, especially if surrogate markers support the diagnosis.

Decision making regarding treatment is much more difficult for patients who do not meet the criteria (18).

Combination of IVIG with aspirin, is efficacious not only in preventing long- term sequelae, but also in relieving the distressing acute symptoms of fever and irritability (19, 20, 21).

Most patients respond to a single dose though cases in this study required retreatment because of persistent symptoms (22, 23). A recent meta-analysis suggested that low- dose aspirin was as effective as high-dose, probably because of its antiplatelet effects (23, 24). We believe this is the second report regarding KD in Iranian children from 1997 to 2004 in Children's Medical Center in Tehran, Iran.

CONCLUSION

KD is an intense life-threatening vasculitis. Kawasaki disease should be considered in any infant or child with a prolonged febrile illness. Associated clinical features, and supportive laboratory data may help in the diagnosis.

Intravenous immunoglobulin and aspirin therapy should be given to patients who meet published criteria, as well as those who do not meet the criteria but have echocardiographic findings consistent with KD.

Also, therapy should be considered in patients who do not meet the criteria and who have normal echocardiograms. Clinicians should weigh up the risks and potential benefits on a case-by-case basis (25).

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