Original Article

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Kawasaki Disease in 159 Iranian Children

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Abstract

Objective: Kawasaki disease (KD) is an intense life-threatening vasculitis. The diagnosis of Kawasaki disease is made by clinical criteria. This disease is a common rheumatologic disease in Iran. The aim of this study was describe the demographics and clinical features of KD in Iranian patients.

Material & Methods: A review was conducted for all cases of KD treated at Pediatric rheumatology department in Children's Medical Center between January 1994 and July 2004. The diagnostic criteria for typical Kawasaki were based on the criteria of the Japan Kawasaki Disease Research Committee. Atypical or incomplete KD has been described in which patients not strictly meeting the diagnostic criteria but have coronary artery changes. Color doppler echocardiograms were done at the time of diagnosis, 14 to 21 days, 60 days, and 1 year after treatment.

Findings: One hundred fifty nine patients were identified. One hundred twenty five children (78.6%) fulfilled criteria for typical KD. Echocardiographic abnormalities were found in 30 cases (18.9%), including 9.6% with typical and 46.1% with atypical Kawasaki. The incidence of atypical Kawasaki in our study was about 22%. Coronary arteries aneurysms found in 66.7% and 33.3% was other abnormalities. Male to female ratio was more in patients with cardiac complication (2.3:1).

Conclusion: Kawasaki disease should be considered in any infants or child (especially less than 2 years old) with a prolonged febrile illness. Demographic features of our patients were similar to reports from other country. The incidence of atypical Kawasaki in our study was about 22%.

Key Words: Kawasaki, Vasculitis, Aneurism, Coronary artery, AtypicalKawasaki

Introduction

Kawasaki disease (KD) is a multisystem, generalized medium and small vessels vasculitis of unknown etiology[1-2], which predominantly affects children under the age of 5 years, and one of most common causes of acquired heart disease among children living in developed countries. About 80% of the patients are under 5 years old between 1 and 5 years of age (mean age is 2.5

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years)[1-2]. Kawasaki disease is more common in males than in females, with a male-to-female ratio of 1.5:1[3].

The disease, was first described in 1967 by Kawasaki based on findings in 50 Japanese children [1-2]. Kawasaki described a unique illness that was characterized by fever, changes in the oropharynx such as fissured lips and strawberry tongue, bilateral conjunctival injection without exudate, cervical lymphadenitis, polymorphic exanthem rash, redness and swelling of the hands and feet, and erythema of the palms and soles[2-4]. In the early 1970s Melish et al reported 12 children from Honolulu with the same illness pattern. Kawasaki disease is now being reported worldwide[5].

In the presence of classic features, many experts believe that the diagnosis can be made with fewer than 5 days of fever or fewer then 4 principal symptoms [4-5]. Laboratory test, anemia, thrombocytosis, leukocytosis, elevated erythrocyte sedimentation rate (ESR), and positive C-ractive protein (CRP), are associated with KD and can support the diagnosis. Coronary artery aneurysms, the most serious consequence of KD, are seen in 20% to 25% of untreated patients, and long-term consequences include coronary stenosis, early coronary stenosis, early atherosclerosis, and myocardial infarction [6-7].

Atypical or incomplete KD has been described in which patients not strictly meeting the diagnostic criteria have coronary artery changes[9-10]. Fortunately, the risk of coronary artery abnormalities decreases by tenfold in patients treated with intravenous immune globulin (IVIG) and aspirin[13-16].

The initial echocardiogram should be obtained as soon as the presence of Kawasaki disease is suspected [7]. This is the study of choice to evaluate for coronary artery aneurysms (CAAs), during the acute stage, obtaining a baseline. Echocardiogram is important to rule out CAAs and evidence of myocarditis, valvulitis, or pericardial effusion. Longitudinal echocardio-graphic follow-up should be repeated in the second or third week of onset of illness, when early coronary dilation will first be noticed in the majority of children who will develop aneurysms. In the absence of significant coronary dilation, cardiac ultrasound may be repeated at approximately 6 to 8 weeks after illness onset. If the echocardiographic findings are abnormal at any point, refer the child to a pediatric cardiologist for a complete cardiac workup and follow-up care.

Atypical or incomplete KD has been described in which patients not strictly meeting the diagnostic criteria but have coronary artery changes [9-10]. Fortunately, the risk of coronary artery abnormalities decreases by ten-fold in patients treated with intravenous immune globulin (IVIG) and aspirin [13-16].

This disease ia s common rheumatologic disease in Iran. The aim of this study was describe the demographics and clinical features of KD at Pediatric Rheumatology department in Children's Medical Center (largest pediatric referral center in Iran).

Material & Methods

All children diagnosed KD in the pediatric rheumatologic department service at Children's Medical Center between January 1994 and July 2004 which were included. Cases were analyzed with respect to the fulfillment of diagnostic criteria, the presence of surrogate markers, echocardiographic findings, and treatment decisions.

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, sex, clinical data, presence and duration of fever and other diagnostic criteria, laboratory test (lowest hemoglobin, highest platelet count, highest pretreatment ESR, positive CRP), echocardiography feature, and outcome, details of treatment and follow-up.

Patients with atypical or incomplete KD have been described in which patients not strictly meeting the diagnostic criteria but have coronary artery changes. These anomalies were also included: aneurysm, dilatation, or ectasia of coronary arteries were seen in echocardiogeraphy [8-9].

Color doppler echocardiograms were done at the time of diagnosis in all cases, and 14 to 21 days, 60 days, and 1 year after treatment. All patients received one doses 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. Follow-up of patients with coronary dilation should be adapted to their clinical course and the severity of lesions and fallow-up in outpatients clinics for all cases more than 5 years.

Findings

One hundred and fifty nine patients were diagnosed with KD during the 10 year period. All cases were included in the study were less than 6 years of age at the onset. Patients ranged from 3 months to 6 years of age, with a median of 2.8 years (Table 1). Seventy five percent (120 cases) of patients were age under 5 years, with 15% (23 cases) under 1 year old at the time of diagnosis, and 10% (16 cases) over 5 years old.

Table 1- Age at onset of KD in 159 patients

Age	No
<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%)**

Eighty-seven patients (55%) were male and 72 (45%) female, Male: Female ratio of 1.2:1. Eighty patients (50%) fulfilled 5 of clinical criteria for KD, 52 cases (32%) fulfilled 4 criteria, 20 cases (12%) fulfilled 3 criteria, and 7 patients (4%) fulfilled 2 criteria.

Seventy percent of these cases were diagnosed within the first 10 days, with and longest time to diagnosis being 25 days. Clinical manifestation and the most important laboratory test were summarized in (Table 2). There are not any positive culture (blood, urine, and throat) in our patients. Other organ involvement in our Kawasaki patients was summarized in (Table 3).

Table -2 Clinical features at onset of KD and laboratory finding in 159 patients

	Findings	No (%)
Clinical features	Fever <5 days	76 (48%)
	>5 days	83 (52%)
	Changes oral cavity and lips	149 (93%)
	Bilateral conjunctiva injection	128 (80%)
	Changes in extremities	100 (62%)
	Polymorphic exanthema	98 (61%)
	Cervical lymphadenopathy	95 (59%)
Laboratory findings	Hb <9 gr/dl	145 (91%)
	Leukocyte count >30,000	150 (94%)
	Platelet count >500,000	127 (79%)
	>700,000	104 (65%)
	ESR > 50	152 (95%)
	> 70- 100	142 (98%)
	C-Reactive protein >3+	145 (91%)
	Abnormal LFT	45 (28%)
	Hypoalbumiemia	25 (15%)
	Leukocyte Synovial Fluid	12 (7%)
	Sterile Pyuria	22 (13%)
	Pleocytosis in CSF	12 (7%)

Coronary or other arterial abnormality were reported in 30 (18.8%), 21 were males and 9 females, (with 2 cases, one girl infant of 3 month and one boy aged 5 years, developed giant aneurysms, lumen diameter >8 mm). Echocardiographic findings were present in 12 patients (9.6%) who had typical Kawasaki, and 18 patients (46.1%) had atypical Kawasaki (in 10 cases who had fever plus 4 criteria, and 8 patients who had fever with 3 criteria for diagnosis of KD). Echocardiographic findings were included definitive aneurysms and ectasia each one in 8 patients, perivascular edema in 6 patients, pericardial effusions in 4 patients, and mitral regurgitation and myocarditis in 2 patients, respectively. Coronary arteries aneurysms resolved in 15 patients (75%) and remained in 5 cases, after 1 year.

Twenty four children (15%) received antibiotics during the course of their illness, because they have not fulfilled with KD criteria. Fifteen patients was treated with methylprednisolone with 30 mg/kg intravenously over 4 hours, administered once daily for 1 to 3 days after two doses of IVIG.

Table 3- Other organ involvement in KD of 159 patients

Organ involvement	No
Persistent fever >10 days	75(47%)
Irritability	127 (79%)
Desquamation of finger tips	97 (61%)
Coronary aneurysms, and ectsia	60 (38%)
Respiratory tract, cough, corisa,	45 (28%)
Erythema & induration at BCG inoculation site	23 (14%)
Gasterointestinal (vomiting and diarrhea)	23 (14%)
Gallbladder hydrops	14 (8%)
Abnormal liver function test	16 (10%)
Genitourinary system (urthritis and 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 (006%)
Beau's line	25 (15%)

By defining the predictive values, patients with a C-reactive protein level >10 mg/dL, LDH level >590 IU/L, and/or hemoglobin value <10 g/dL are considered non-responsive to IVIG.

Discussion

KD is a generalized vasculitis of unknown etiology, and mainly affects young children. There is no specific test for diagnosis of KD [1-3]. The diagnosis is established by meeting certain criteria [4]. According to the Japanese diagnostic guideline of KD, a diagnosis is made on the recognition of five or six main symptoms. If only four main symptoms are found, which echocardiography or angiography reveals coronary arterial changes; the Japanese diagnostic guideline also recognizes the disease as KD [5-7]. None of the clinical features of Kawasaki disease is pathognomonic. For this reason, the diagnosis of Kawasaki disease requires exclusion of other illnesses that might mimic its clinical features. These include streptococcal and staphylococcal toxin-mediated illness; infection with adenovirus, enterovirus, or measles; and systemic allergic reactions to various medications.

Typical Kawasaki disease has a well-characterized clinical course[8-10].. In our series all of children with Kawasaki disease generally were irritable and uncomfortable. Fever was usually high and spiking, exceeding 39ºc in almost all cases, compared with the previous reports. Conjunctive injection were seen more prominently bulbar than palpebral without associated exudates compatible with others series [11]. Oropharyngeal changes were seldom associated with red lips, strawberry tongue and pharyngeal less than previous reported. The rash erythematous and diffuse maculopapular were similar with others reports. Urticaria, scarletini-form rash rarely occur in our series. Extremity changes were striking, with indurations and erythema beginning abruptly at the wrists or ankles. Lymphadenopathy usually unilateral, it was seen in the course of disease in our series [12-13]. Subsequent periungual, desquamation occurred in all cases 2 to 3 weeks after onset of fever compared with previous series.

Most clinical manifestation of our series was diagnosed in 1-2nd week of illness. Cardiac abnormalities occur in the 2nd to 4th week of illness [14]. In our series approximately 30 cases (18%) developed cardiac problems. These finding including CAAs, arterial ectasis, pericarditis with pericardial effusion, acute myocarditis, congestive heart failure (CHF), and mitral insufficiency that were seen more than others reported [7-9].

Aneurysms developed in only 2 cases that treated with intravenous gamma globulin before the 10th day of illness. Facial nerve palsy occur in one girls <2 years old with active KD, and resolved in 1 to 2 weeks after treatment with IV IG [14-15].

KD has many other manifestations that reflect its systemic nature. Arthritis persists of our series, and often involved the small joints of the

fingers and toes. Arthritis appears more common in girls than in boys [8-12]. Urethritis with sterile pyuria present in our groups. Mild hepatitis with 2-to-4-fold elevations of transaminases occur in this report. Hydrops of the gallbladder occurs in <8% of cases and may cause severe right upper quadrant pain.

The medical management of KD involves the use of gamma globulin and aspirin as anti-inflammatory agents and long-term anticoagulation. IVIG with aspirin dramatically changed the management of KD. Some controversy exists about the ideal timing to begin gamma-globulin, but that is not an issue that concerns emergency physicians. Treatment is more effective if started within 10 days of onset of fever [16-18]. Delays in diagnosis and treatment, which occur more frequently in older children, are associated with an increased risk of coronary artery aneurysms.

If a child clearly meets criteria for KD, the decision to treat with IVIG is not difficult, especially if surrogate markers support the diagnosis. The classic dosage is 400 mg/kg/d IV in a single daily infusion for 4 d or single dose of 2 g/kg IV infused over 12 h. Combination of IVIG with aspirin, with dose 80-100 mg/kg/d PO divided qid for 2 wk initial; 3-5 mg/kg PO qd for 6-8 wk maintenance [15].

If the coronary artery abnormalities were detected by echocardiogeraphy continue the aspirin with dose 3-5 mg/kg PO qd long term [19]. Most patients respond to a single dose, though cases in this series require retreatment because of persistent symptoms and might repeat course of therapy in those who do not have an adequate response to initial treatment [16-18].

Reinfusion of 2 g/kg is administered when fever persists or recrudesces 48 hours or more after termination of the initial IVIG infusion. Multiple IVIG infusions are sometimes administered to patients with especially severe disease [22-23].

The subgroup of patients with KD resistant to IVIG therapy is at greatest risk for development of coronary artery aneurysms and long-term sequelae of the disease. Additional therapy at early stage of the disease should be considered for patients who are predicted to be IVIG non-responsive [24,25]. A recent meta-analysis suggested that low-dose aspirin was as effective as high-dose, probably because of its antiplatelet effects [23, 24].

Generally, 5% of children with Kawasaki disease are still at risk for CAAs despite timely IVIG therapy. The incidence of cardiac complication in our study was 18.9%, but with treatment this rate decreased to 3.1%. Further studies are needed to assess the risks and benefits of steroid administration in KD.

Infants and school-age children displaying an incomplete or atypical disease are at higher risk because of the lack of awareness of occurrence of the disease at this age. IVIG remains the gold standard of treatment to prevent CAAs, though 10–15% of children require additional infusion and steroids or immunesuppressants, and eventually biological drugs. Intravenous immune globulin and aspirin therapy should be given to patients who meet published criteria, as well as to those who do not meet criteria but have echocardiographic findings consistent with KD.

Conclusion

Demographic features of our patients were similar to reports from other country. Kawasaki disease should be considered in any infants or child (especially less than 2 years old) with a prolonged febrile illness. The incidence of atypical Kawasaki in our study was about 22%. Male to female ratio of patients was 1.2:1, but the coronary or other arterial abnormality was 2.3:1.

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