The experience with 113 patients with Kawasaki disease in Fars Province, Iran

Ali Akbar Asadi-Pooya, Mohammad Borzoee, Hamid Amoozgar
Department of Pediatrics, Shiraz Medical School, Shiraz, Iran

SUMMARY: Asadi-Pooya AA, Borzoee M, Amoozgar H. The experience with 113 patients with Kawasaki disease in Fars Province, Iran. Turk J Pediatr 2006; 48: 109-114.

This study was conducted to determine the epidemiology, clinical manifestations, cardiac involvements and laboratory findings of Kawasaki disease (KD) in Fars Province, Iran from January 1991 to December 2002. One hundred and thirteen patients with KD were confirmed. This syndrome occurred mostly in males (ratio=2.1:1). The most commonly affected age group was one to five years old. There was no secondary case in families, none of the patients were related and recurrence of disease was seen in only one patient. Prolonged fever and thrombocytosis were significant risk factors for developing coronary artery disease ($p<0.05$, respectively). Among the 10 patients with cardiac involvement, seven patients had dilated coronary arteries (>4 mm) and three patients had aneurysm of coronary artery in their first echocardiography. It has been suggested that a high index of clinical suspicion of KD could improve diagnosis and implementation of preventive treatment.

Key words: epidemiology, Iran, Kawasaki disease, manifestations.

Kawasaki disease (KD) is an acute febrile mucocutaneous lymph node syndrome with multisystem vasculitis mainly affecting infants and small children under five years of age[1].

Kawasaki disease was first described by Dr. Tomisaku Kawasaki in 1967[2], and shortly thereafter was found to be an important cause of heart disease in children. It has replaced rheumatic fever as the most common cause of acquired heart disease in children in North America and Japan. Almost 117,000 cases of KD were reported in Japan through 1992, but KD occurs worldwide[3]. The disease has been reported in more than 60 countries around the world and some countries, in addition to Japan, have experienced epidemics[4].

The diagnostic criteria for KD, developed first in Japan, include fever of at least five days' duration, typically with at least four of the following five features: 1) bilateral conjunctival injection; 2) inflammatory changes of the lips, tongue (strawberry tongue), and pharynx; 3) changes of peripheral extremities, particularly redness and swelling of the hands and feet, with subsequent periungual desquamation; 4) rash, primarily truncal and taking many forms, but non-vesicular; and 5) cervical lymphadenopathy, usually unilateral. The illness should not be explained by other known disease processes[5]. The clinical features do not need to be present simultaneously and, especially in infants, may be subtle and present only for a brief time. Patients with fever and three of the features can be diagnosed with classic KD by these criteria if coronary artery abnormalities are seen on echocardiogram or angiography[6].

Much remains unknown about the etiology of KD. Clinical and epidemiologic features of KD point to an infectious cause, most likely a single etiologic agent or a closely related group of agents. In acute KD, both the T- and B-lymphocyte immune responses, the cornerstones of acquired immunity, are oligoclonal, indicating a response to a conventional antigen rather than a superantigen[7].

Although much is still not known about KD, there have been major advances in the treatment of this disease. In Newburger et al.'s[8]

1986 report, children were randomized to receive the standard therapy of high-dose salicylates, or high-dose salicylates plus four days of 400 mg/kg intravenous immunoglobulin (IVIG) per day. On blind echocardiographic reading, the development of coronary abnormalities was reduced by about 85% using the latter therapy.

This study was conducted to determine the epidemiology, clinical manifestations, cardiac involvements and laboratory findings of KD in Fars Province, Iran, from January 1991 to December 2002.

Material and Methods

In this cross-sectional study, all KD patients reported in Shiraz University Hospitals (Nemazee, Faghihi and Dastgheib Hospitals) from January 1991 to December 2002 were analyzed to define the characteristics, clinical manifestations, cardiac involvements, laboratory data and method of management. Because only these University Hospitals have pediatric wards in Shiraz, these patients represent an accurate number of KD patients reported in this period. The criteria to confirm the diagnosis were based on the patients' clinical features. Demographic, clinical and para-clinical information was collected by referring to the patients' files.

Of 120 probable patients admitted as having KD, 113 fulfilled the criteria and had definitive KD. Only these 113 patients were included in the study.

The data from patients were kept confidential through codes. Statistical analysis was done by t-test and chi-square. A p value less than 0.05 was considered as significant.

Results

Clinical manifestations

Totally, 113 patients were studied during a 12-year period. There were 77 males (68.1%) and 36 females (31.9%) (male to female ratio= 2.1:1). Of 10 patients with coronary cardiac diseases, 7 (70%) were male and 3 (30%) were female, but this was not significantly different from patients without cardiac involvement (p>0.05).

The youngest reported patient was a five-month-old female and the oldest a 13-year-old male. The mean age of the patients was 3.89 years. Seventy percent of patients were one to five years old.

More patients were seen during winter and spring than summer and autumn but the difference was not significant (p>0.05). The peak incidence was in February and October and lowest incidence in January, June and August (Fig. 1).

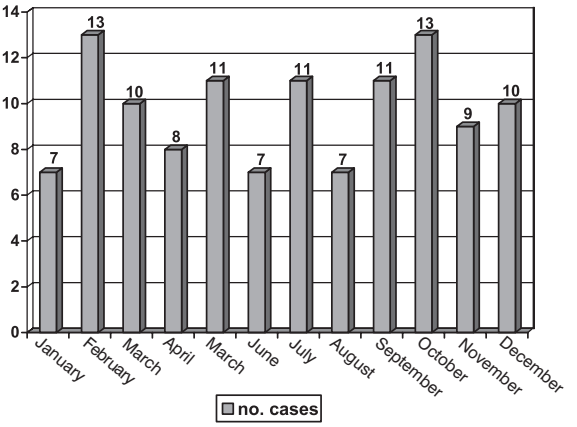

Fig. 1. Monthly distribution of 113 KD patients in Fars Province, Iran.

The median temperature in these patients was 39.4°C, and 70% of the patients had a temperature of more than 39°C. The mean duration of fever was 9.14 days, and it was not significantly different in cardiac and non-cardiac groups (p>0.05).

The mean duration to diagnosis of disease from the onset of the first symptom was seven days, with longest time to the diagnosis being 45 days. Seventy-five percent of the patients were diagnosed within the first 10 days. Time to the diagnosis differed for cardiac (median 10 days) and non-cardiac (median 7 days) groups, though not significantly (p>0.05).

One hundred and seven (94.6%) patients had conjunctivitis; it was non-purulent in 101 (89.3%) patients. Oral changes were seen in 106 (93.8%) patients. The most commonly reported changes were red lips, and fissuring, cracking or bleeding of the lips. Changes in the extremities (including erythema, edema and desquamation) were reported in 58 (51.3%) patients. Rash was reported in 91 (80.5%) patients, most commonly as maculopapular, scarlatiniform and morbiliform, but erythema multiforme and urticarial rashes were also reported. Cervical lymphadenopathy was reported in 74 (65.4%) of the patients, and was

cervical in 98.6% of the patients. Periungual desquamation was reported in 47 (41.5%); the mean time of onset of the desquamation from beginning of the illness was 12.95 days. Clinical manifestations of the patients studied are presented in Table I.

Table I. Spectrum of Clinical Manifestations in 113 KD Patients Studied

Physical sign	Number of patients/Total	Percent
History of fever	113/113	100
Conjunctivitis	107/113	94.6
Oral changes	106/113	93.8
Fever (>38°C)	104/113	92
Cutaneous rash	91/113	80.5
Cervical lymphadenopathy	74/113	65.4
Extremity changes	58/113	51.3
Irritability	37/113	32.7
Diarrhea	33/113	29.2
Arthritis	28/113	24.7
Tenderness at hepatic lodge	7/113	6.2
Meningeal irritation	7/113	6.2

Laboratory findings

The median erythrocyte sedimentation rate (ESR) was 53 mm/hour, with ESR greater than 80 in 25% of the patients. Median ESR in the cardiac group was 64 mm/hour; it did not differ significantly from that of the non-cardiac group ($p>0.05$).

The median white blood cell (WBC), neutrophil, monocyte, eosinophil and band counts were not significantly different in cardiac and non-cardiac groups ($p>0.05$ for all). The median platelet count was 458×10^9/L, with thrombocytosis (platelet $>450\times10^9$/L) in 51 (45.9%) of the patients. The median platelet count in the cardiac group was 777.5×10^9/L, and this was significantly higher in comparison to the non-cardiac group ($p<0.05$). Laboratory findings in the patients studied are presented in Table II.

Among the 10 patients with cardiac involvement, seven had dilated coronary arteries (>4 mm) and three patients had aneurysm of coronary artery in their first echocardiography. Pericardial effusion was detected in two patients. All of these 10 patients had mitral regurgitation and

Table II. Spectrum of Laboratory Findings in 113 KD Patients Studied

Laboratory finding	No. positive/No. tested	Percent
Leukocytosis: white blood cell count/mm^3		
>10,000	87/112	77.6
>15,000	42/112	37.5
>20,000	17/112	15.1
Absolute neutrophil count/mm^3		
>2500	102/105	97.1
>5000	86/105	81.9
>10,000	66/105	62.8
Absolute band count/mm^3		
>500	21/105	20
Eosinophilia (>450/mm^3)	18/104	17.3
ESR>30	90/105	85.7
Thrombocytosis (platelet>450,000/mm^3)	68/111	61.3
Hyperbilirubinemia	11/52	21.1
Direct hyperbilirubinemia	7/11	63.6
SGOT elevation	14/52	26.9
SGPT elevation	12/52	23
Pyuria	56/111	50.5
Hematuria	11/111	9.9
Anemia (hemoglobin<12 g/dl)	82/111	73.9

ESR : Erythrocyte sedimentation rate.
SGOT: Serum glutamic-oxaloacetic transaminase.
SGPT : Serum glutamic-pyruvic transaminase.

six patients had tricuspid regurgitation as well. Dilated coronary artery had regressed in four patients in the second echocardiography, almost four weeks after the first, but it was persistent in the remaining three for at least two months.

Management

Treatment used in these patients was a varying combination of IVIG and aspirin. In total, 110 (97.3%) patients received IVIG (2 g/kg in single dose or divided in 4 days). Median number of days of IVIG administration from the beginning of their disease was 10, but in the non-cardiac group the median was seven days. One hundred and five patients (92.9%) received aspirin (anti-inflammatory doses). Ninety-two (81.4%) children also received antibiotics during the course of their illness.

The mean duration of fever after starting aspirin and IVIG was 2.23 days in non- cardiac patients and four days in cardiac patients (not significant; $p>0.05$). Seven patients did not fulfill the criteria for KD but were treated as having KD by IVIG and aspirin.

Discussion

The male preponderance and age distribution in this study are similar to reports from Japan, the British Isles, the United States and Australia, with a slightly greater male to female ratio in this study (2.1:1 in comparison to 1.5:1 in Japanese children with KD)[9-12].

In this study, similar to the Japanese study, KD was common throughout the year in contrast to the report by Bell et al.[11] showing a peak of seasonal incidence of KD in winter and spring[9]. Absence of clear-cut seasonal differences has been reported in some previous studies, specifically after 1987[4].

Recurrence of disease was seen in only one patient five years after the first admission. In this study, there were no secondary cases in families, and none of these patients were related. In a Japanese study, the proportion of patients with a family history of KD among siblings was approximately 1% in all years, far higher than one might expect from the incidence rate in the general population[13].

The absence of seasonality changes in the incidence of KD and the absence of secondary cases in families negate the theory of an infectious agent as the causal agent of KD. However, many epidemiologic features of KD are consistent with an infectious cause. These include the young age group affected and the occurrence of epidemics with a geographic wave-like spread of the illness during the epidemic. The rarity of KD in young infants less than three months of age and the virtual absence of the disease in adults fit best with the hypothesis that a ubiquitous infectious agent causes KD, with the youngest infants protected by passive maternal antibody and widespread immunity present among adults. In addition, the clinical features of abrupt onset of illness in previously well children, characterized by prolonged high fever, conjunctival injection, oral mucosal changes, rash, and cervical lymphadenopathy strongly support an infectious cause. Because these symptoms generally resolve within 1-2 weeks even without treatment and generally do not recur, an infectious rather than an autoimmune etiology seems most likely. KD affects all ethnicities and racial groups worldwide. However, the higher attack rate observed among Asians strongly suggests that genetic factors play a role in the expression of clinical disease[7].

Cardiac involvement was seen in 8.8% of our patients and the percentage for those with cardiac sequelae was 5.3%, which is consistent with the recent reports with the same managements. The proportion of cardiac events in this study was more among males, as in previous reports[4]. Thrombocytosis at the time of diagnosis was a significant risk factor for developing coronary artery disease in this study, which may be due to the late diagnosis of KD in cardiac patients that synchronized with thrombocytosis. This finding is in contrast with the report by Honkanen et al.[14], who found that the degree of anemia, platelet count, ESR and WBC count were not shown to be predictive of coronary artery sequelae. In our study, similar to previous studies, prolonged fever was a risk factor for coronary artery abnormalities[14].

Many infectious diseases mimic KD. Indeed, the distinction between KD and infectious diseases is problematic in most children. Physicians visited all of our patients, but most of the patients had received various antibiotics including penicillin, ampicillin, amoxicillin, cephalothin, erythromycin, gentamycin and

trimethoprim-sulfamethoxazole. Results from laboratory investigations (WBC, ESR, platelet count, etc.) in this and other studies indicate that a large proportion of children did not have abnormal results at the time of testing and that there are no specific and diagnostic laboratory findings in KD. The diagnosis of KD is based on clinical features and supporting laboratory and echocardiographic findings. Revised guidelines for the diagnosis of incomplete KD are being developed, but until a diagnostic assay is available, a low threshold for therapy is required to avoid potentially devastating sequelae. It is also important to consider other diagnoses, which may mimic many of the symptoms, in the evaluation of KD. The differential diagnosis may include scarlet fever, drug hypersensitivity reactions, Stevens–Johnson syndrome, toxic shock syndrome, adenoviral infection, Epstein–Barr virus (EBV) infection, leptospirosis, juvenile rheumatoid arthritis, measles, and others. Several of these disease processes have specific diagnostic tests (such as serum IgM for measles). Patients with scarlet fever usually have a positive throat culture for Group A streptococcus and a prompt response to penicillin or other β-lactam agents. Historical features may help in the evaluation of other diagnoses, such as exposure risks for leptospirosis and medication history for drug hypersensitivity reactions. Stevens–Johnson syndrome can usually be distinguished by the ulcerative mucosal lesions and/or bullous skin lesions that are absent in KD. Toxic shock syndrome usually has a more abrupt onset with profound hypotension and several laboratory abnormalities that are usually not present in KD (such as renal dysfunction and elevated creatinine phosphokinase [CPK]); however, rarely it may be very difficult to distinguish between these diagnoses, and treatment for both may be necessary. Unusual presentations of juvenile rheumatoid arthritis also may be difficult to distinguish from incomplete KD, and the diagnosis may become clear only after the patient fails to respond to IVIG therapy[6]. In any case, until an effective diagnostic test for KD is developed, sensitivity has a somewhat higher priority than specificity for guidelines and recommendations, since treatment is safe and effective in reducing potentially devastating sequelae. Despite current recommendations that all children with KD should receive IVIG within the first 10 days of the onset of fever[15-20], we are concerned that 25% of the patients in this study were diagnosed after 10 days.

Acknowledgement

The authors thank Dr. K. Asadi-Pooya and Dr. M. Hashemi-Nasab for their great assistance. This work was supported by Shiraz University of Medical Sciences.

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous lymph node syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children [in Japanese]. Jpn J Allerg 1967; 16: 178-222.
2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagava H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974; 54: 271-276.
3. Cook DH, Anita A, Attie F, et al. Results from an international survey of Kawasaki disease in 1979-1982. Can J Cardiol 1989; 5: 389-394.
4. Nakamura Y, Yanagawa H. The worldwide epidemiology of Kawasaki disease. Prog Ped Cardiol 2004; 19: 99-108.
5. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993; 87: 1776-1780.
6. Rowley AH, Shulman ST. Kawasaki syndrome. Pediatr Clin North Am 1999; 46: 313-329.
7. Rowley AH. The etiology of Kawasaki disease: a conventional infectious agent. Prog Ped Cardiol 2004; 19: 109-113.
8. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki disease with intravenous gamma globulin. N Engl J Med 1986; 315: 341-347.
9. Morens DM, Anderson LJ, Hurwitz Es. National surveillance of Kawasaki disease. Pediatrics 1980; 65: 21-25.
10. Pierre R, Sue-Ho R, Watson D. Kawasaki syndrome in Jamaica. Pediatr Infect Dis J 2000; 19: 539-543.
11. Bell DM, Morens DM, Holman RC, Hurwitz ES, Hunter MK. Kawasaki syndrome in the United States, 1976-1980. Am J Dis Child 1983; 137: 211-214.
12. Royle JA, Williams K, Elliott E, et al. Kawasaki disease in Australia. Arch Dis Child 1998; 78: 33-39.
13. Fujita Y, Nakamura Y, Sakata K, et al. Kawasaki disease in families. Pediatrics 1989; 84: 666-669.
14. Honkanen VE, McCrindle BW, Laxer RM, Feldman BM, Schneider R, Silverman ED. Clinical relevance of the risk factors for coronary artery inflammation in Kawasaki disease. Ped Cardiol 2003; 24: 122-126.
15. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gammaglobulin as compared with four infusions in treatment of acute Kawasaki syndrome. N Engl J Med 1991; 324: 1633-1639.
16. Rowley AH, Shulman ST. Current therapy for acute Kawasaki syndrome. J Pediatr 1991; 118: 987-991.

17. American Academy of Pediatrics Committee on Infectious Disease. Intravenous gammaglobulin use in children with Kawasaki syndrome. Pediatrics 1988; 82: 122.

18. Shulman ST. Management of Kawasaki syndrome: a consensus statement prepared by North American participants of the third international Kawasaki disease symposium,Tokyo, Japan, 1988. Pediatr Infect Dis J 1989; 8: 663-665.

19. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993; 87: 1776-1780.

20. Rowley AH, Shulman ST. What is the status of intravenous gammaglobulin for Kawasaki syndrome in the United States and Canada? Pediatr Infect Dis J 1988; 7: 463-466.