Varying clinical features of Turkish Kawasaki disease patients

Bora Gülhan[1], Selman Kesici[2], Serdar Beken[2], Erman Çilsal[2], Gülsev Kale[2], Dursun Alehan[3], Ateş Kara[4], Seza Özen[1]

Divisions of [1]Pediatric Nephrology, [3]Pediatric Cardiology, and [4]Pediatric Infectious Diseases, [2]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Gülhan B, Kesici S, Beken S, Çilsal E, Kale G, Alehan D, Kara A, Özen S. Varying clinical features of Turkish Kawasaki disease patients. Turk J Pediatr 2012; 54: 1-6.

Kawasaki disease (KD) is an acute, systemic and self-limited vasculitis that is complicated with the development of coronary artery (CA) aneurysms. We present the clinical features of Turkish KD patients from a tertiary referral center. When 33 KD patients were assessed, a number of features stood out as differing from the expected, for example, periungual peeling 7.5±7.5 days after fever onset - 42.4% of patients had periungual peeling within 14 days after fever onset. CA involvement was detected at an average of 12.3±7.9 days after fever onset. Fifty percent of the patients had been diagnosed to have CA involvement within eight days after the onset of fever. The performance of criteria suggested by American Heart Association was satisfactory, with 19 of 29 patients (65.5%) having three or more of the required laboratory features (sensitivity 65.5%). We believe Turkish patients may present differences in the course of KD.

Key words: Kawasaki disease, clinical features, laboratory criteria.

Kawasaki disease (KD) is an acute, systemic and self-limited vasculitis that may be complicated with the development of coronary artery (CA) aneurysms. It occurs predominantly in infants and young children. After the initial description by Dr. Kawasaki in 1967, the disease is now widely known to occur in both endemic and community-wide epidemic forms in America, Europe and Asia in children of all races[1]. In 1967, Dr. Kawasaki described the clinical features of the disease that now comprise the diagnostic criteria for KD. These criteria include fever persisting for at least five days and presence of four of the five principal clinical criteria: changes in extremities, polymorphous exanthem, bilateral non-purulent conjunctival injection, changes in lips and oral cavity, and cervical lymphadenopathy[2]. Some patients have prolonged fever plus two or three of the diagnostic criteria. In this case, incomplete KD should be suspected. Recognition of incomplete cases is especially important for infants aged <6 months.

In the United States, KD is the leading cause of acquired heart disease[3]. CA aneurysms or ectasia develops in 15-25% of untreated children with the disease and may lead to myocardial infarction, sudden death or ischemic heart disease[4]. Treatment with intravenous immunoglobulin (IVIG), if administered within the first 10 days of illness, reduces the prevalence of CA aneurysms five-fold[5,6]. Treatment after 10 days increases the risk of CA aneurysm nearly three-fold when compared with earlier treatment[7]. This fact suggests that CA aneurysm is not expected before the tenth day.

Although not as common as in Asian countries, KD is also an important health problem in our country. In a nationwide study conducted by Ozen et al.[8], KD was the second most common vasculitis in childhood (9% among the pediatric vasculitides registered). The purpose of the present study was to determine the patient characteristics and different clinical features of KD in a tertiary referral center in Turkey. We also aimed to evaluate the sensitivity of the minor criteria proposed by the American Heart Association (AHA) in patients with a confirmed diagnosis of KD.

Material and Methods

Patients

From September 2007 to May 2010, all KD patients were evaluated by a study group at Hacettepe University, İhsan Doğramacı Children's Hospital, a tertiary referral center. The Kawasaki Study Group (KSG) consists of specialists from different departments who work in the care of KD, namely pediatric cardiology, pediatric rheumatology and pediatric infectious diseases. The task of the KSG is to evaluate all patients suspected to have KD, make appropriate treatment plans, and follow them to the adult period, if required. All patients who have prolonged fever (more than 5 days) with any evidence that suggests KD were evaluated by this group. This group decided on the final diagnosis and management of all the presented patients.

Data Collection

Demographic data that were collected on the registration form included age at presentation, gender and ethnicity. Clinical data included the main complaint, initial diagnosis of the patient, number of illness days from onset of fever to diagnosis of KD, and presence or absence of KD criteria. Laboratory data included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Laboratory parameters suggested by the AHA to evaluate suspected incomplete KD cases were also evaluated[1]. The AHA has suggested that the presence of at least three parameters indicates KD. These parameters are: low albumin, elevated alanine aminotransferase (ALT), low hemoglobin, increased platelet counts after ≥7 days, and increased white blood cell (WBC) count and urinary WBCs in high-power field (HPF). Hypoalbuminemia was defined as that below ≤3 g/dl. Urinalysis was performed for pyuria (≥10 WBC/HPF). Complete blood cell count indices were also evaluated. Hemoglobin levels were measured, and anemia was defined according to limits for age. Platelets were measured after seven days of illness, and thrombocytosis was defined for levels ≥450,000/mm^3. WBC counts were measured and levels more than ≥15,000/ mm^3 were registered. The upper limit of CRP was 0.5 mg/dl and that of ESR was 20 mm/hr. Echocardiography was performed in all patients. Response to treatment was also assessed. Unresponsiveness to treatment was defined as the persistence or recrudescence of fever 36 hours after IVIG treatment[1]. Incomplete KD was defined as the presence of less than four of the five KD criteria.

Statistical Analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 11.0.

Results

During the 32-month period, 43 patients were evaluated by the KSG. Thirty-three of 43 patients had prolonged fever and fulfilled at least four criteria and were therefore confirmed as KD. None of the patients met less than four criteria. In 10 patients, the final diagnosis was not KD. Their final diagnoses were as follows: upper respiratory tract infection (4 patients), Epstein-Barr virus (EBV) infection (2 patients), bacterial sepsis (2 patients), hemophagocytic lymphohistiocytosis (1 patient), and polyarteritis nodosa (1 patient).

Demographical and Clinical Data

Thirty-three patients (18 girls, 15 boys) were diagnosed as KD. The male to female ratio was 0.83. The age range of the patients was 5 months-9.5 years, and mean and median values were 39.2±32.5 months and 24 months, respectively (Fig. 1). The main complaint of the patients (30/33) was prolonged fever. The mean and median durations of fever were 9.4±6.2 days and 7 days, respectively. Only 3 patients (10.7%) had a different presenting complaint. These complaints were swelling of

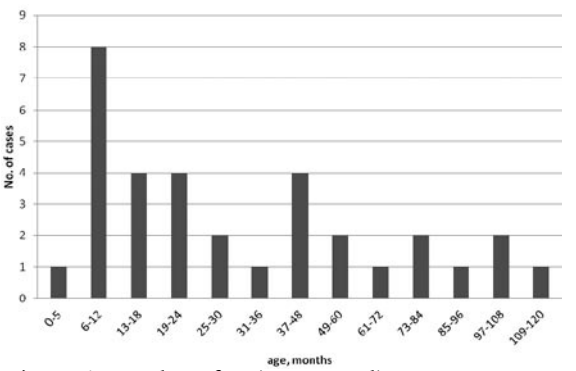

Figure 1. Number of patients according to age groups.

extremities, maculopapular rash, and swelling of the abdomen and scrotum, respectively. All 3 patients also had prolonged fever in their medical history.

Most patients were admitted to hospitals during winter months (November, December, January, February) (15/33; 45.4%) and spring months (March, April, May) (9/33; 27.2%).

Nine of 33 patients (27.2%) were less than one year of age (mean: 10 months), and they had mean and median durations of fever of 11.0±5.4 and 10 days, respectively (minimum: 5, maximum: 20 days). The rest of the patients had a mean and median duration of fever of 8.8±6.5 and 6 days, respectively (minimum: 1, maximum: 30 days). The difference between the two groups was statistically insignificant.

The frequency of KD criteria among this cohort was as follows: changes in lips and oral cavity, 93.9%; changes in extremities (either indurative edema of extremities or desquamation of skin of hands, feet and perineum), 78.8%; bilateral bulbar non-purulent conjunctival injection, 72.7%; polymorphous exanthem, 69.7%; and cervical lymphadenopathy, 66.7%. Twenty-one of 33 patients (63.6%) had periungual peeling of fingers or toes. Periungual peeling of fingers or toes started 7.5±7.5 days after fever onset (median: 6 days). Fourteen of 33 patients (42.4%) had periungual peeling within 14 days after fever onset.

Laboratory Data

All patients except one had increased ESR. Mean and median levels for ESR were 66.4±30.9 mm/hr and 70 mm/hr, respectively. Four patients (14.2%) had ESR >100 mm/hr (minimum and maximum levels: 8 mm/hr and 140 mm/hr, respectively). Similarly, all patients had increased CRP levels (mean: 9.6±9.2 mg/dl; median: 8.2 mg/dl). Minimum and maximum levels for CRP were 0.1 mg/dl and 34 mg/dl, respectively.

As to the AHA criteria, thrombocytosis after seven days was the most common laboratory criterion (25/33; 75.8%) present in our patient cohort. The second most common was elevation in ALT (21/33; 63.6%). The percentages of other criteria were as follows: WBC count ≥15,000/mm^3: 51.5% (17/33), anemia for age: 51.5% (17/33), pyuria: 25% (7/28), and hypoalbuminemia: 12.1% (4/33) (Table I).

According to the AHA criteria, laboratory tests should be assessed for patients with suspected incomplete KD when they have characteristics of KD. When they have CRP ≥3.0 mg/dl and/or ESR ≥40 mm/hr, supplemental laboratory criteria should be checked, and patients with ≥3 criteria should be treated[1]. At presentation, 29 of 33 children (87.8%) with definite KD had ESR ≥40 mm/hr and/or CRP ≥3.0 mg/dl. Nineteen of 29 patients (65.5%) had ≥3 of the required laboratory criteria (sensitivity 65.5%).

The diagnosis of KD for patients under the age of one deserves special attention. In our patient cohort, there were 9 patients (5 female, 4 male) aged ≤1 year. In this group, 6 of 9 patients had CA involvement related to the disease. All of these patients had increased acute phase reactants (CRP ≥3.0 mg/dl and/or ESR ≥40 mm/hr). When supplemental laboratory criteria suggested by the AHA were tested for this cohort, 7 of 9 patients had ≥3 of the required laboratory criteria (sensitivity 77.7%).

Cardiological Data

Fourteen of 33 patients (42.4%) had CA involvement. Patients were divided into three groups according to changes in CA. Group 1,

Table I. Number and Percentage of Patients with Positive Laboratory Criteria

Supplemental laboratory criteria	No. of patients (%)
Thrombocytosis after seven days of illness	25/33 (75.8%)
Elevation of ALT	21/33 (63.6%)
White blood cell count ≥15,000/mm^3	17/33 (51.5%)
Anemia for age	17/33 (51.5%)
Pyuria	7/28 (25%)
Hypoalbuminemia	4/33 (12.1%)

ALT: Alanine aminotransferase.

without CA changes (n=19), Group 2 (n=10) with mild CA dilatation (≤5 mm), and Group 3 (n=4) with significant CA aneurysms (>6 mm). Only 1 patient had giant aneurysm (>8 mm) with thrombosis.

In this cohort, CA involvement had started relatively early after the onset of fever. CA involvement was detected at an average of 12.3±7.9 days after fever onset (minimum: 5 days, maximum: 33 days, median: 10 days). Fifty percent of the patients (7/14) were diagnosed to have CA involvement within eight days after the first fever during the follow-up period.

Response to Treatment

Intravenous immunoglobulin (IVIG) was given to all patients as a single dose of 2 g/kg and all received acetyl salicylic acid (80-100 mg/kg/day, in 4 divided doses). 7.1% of the patients (2/28) did not respond to the first dose of IVIG and received a second dose. A short course of steroids was administered for persistent ESR and CRP.

Discussion

Vasculitides sometimes present different features and courses in different ethnic groups. For example, Takayasu arteritis is known to affect the thoracic aorta more often in European patients, whereas abdominal aorta is more commonly involved in Asians[9]. A pediatric international group had shown that the organ involvement in Behçet's disease displayed differences among Turkish, Arabic and French patients[10]. In this single-center study, two different characteristics of KD stand out in our Turkish patients: earlier occurrence of desquamation and earlier occurrence of cardiovascular disease, before that expected in conventional teaching.

From a classical point of view, erythema of palms and soles and edema of hands and feet can be observed in the acute phase of the syndrome. As a late manifestation of the disease, two or three weeks later, periungual peeling of the fingers could be observed. Desquamation of fingers prompts healthcare providers to consider a missed diagnosis, especially in a child with antecedent febrile illness. Similar desquamation was reported for patients recovering from toxic shock syndrome and with streptococcal toxins (e.g., scarlet fever)[11]. In our series, periungual desquamation started in a relatively early period. This situation could not be explained with the delayed diagnosis of the KD, since in 42.4% of the patients, peeling of fingers or toes started within 14 days after fever onset. Thus, Turkish patients seem to develop this feature earlier. In a group of patients, recurrent peeling episodes can be observed for several years after their recovery. Michie et al.[11] reported that 11% of the patients have recurrent peeling after suffering from KD.

Cardiovascular manifestations are the leading cause of long-term mortality and morbidity. The pericardium, myocardium, endocardium, valves, and CAs may all be involved. Echocardiography is an important diagnostic tool especially for the CA involvement. However, a normal echocardiogram does not exclude KD because coronary lesions usually occur in the late convalescence period of the disease. The development of the coronary lesions may be delayed as late as 6-8 weeks after the onset of fever[12,13]. However, in our patient cohort, half of the patients developed CA involvement within eight days after the first fever peak. This points to the importance of timely diagnosis of KD because the major sequelae of KD are related to the CA system. The mainstay of treatment of KD is IVIG, which should be instituted within the first 10 days of illness and, if possible, within 7 days of illness[1]. However, this time period should be shorter for Turkish patients because they develop cardiac complications much earlier.

In our patient cohort, the male to female ratio was 0.83, which is less than that reported in case series in the literature, in which the ratio was approximately 1.5 to 1.7:1[4,5]. The median age was two years, which was similar to admissions for KD in the United States[14]. In our series, 9 (27.2%) patients were less than one year of age. Their mean duration of fever was longer than in older patients (11.0±5.4 days vs. 8.8±6.5 days).

Despite many decades of research after the definition of KD, no causative pathogen or environmental trigger has been identified. Triggering of an infectious agent in a generally predisposed child may result in the disease

[15]. This infectious theory is supported by the seasonality, with winter and spring peaks in most temperate countries and summer peaks in many countries in Asia[1]. Most of our cases presented in winter and spring months when most infectious agents were more common.

The American Academy of Pediatrics has proposed a diagnostic algorithm for patients who have fever lasting more than five days with two or three clinical criteria. Although these are not a part of classical diagnostic criteria for KD, they are recommended for incomplete cases or for infants ≤6 months old on day ≥7 of fever without another explanation[1]. According to that algorithm, incomplete cases in which ESR is ≥40 mm/hr and/or CRP is ≥3 mg/dl, supplemental laboratory criteria should be checked. Those laboratory criteria include: albumin ≤3 g/dl, anemia for age, elevation of ALT, platelets after 7 days ≥450,000/mm^3, WBC ≥15,000/mm^3, and ≥10 WBC/HPF in urinalysis. In the study conducted by Yellen et al.[16], performance of the 2004 AHA recommendations for treatment of KD was evaluated. They concluded that application of the 2004 recommendations improves the rate of IVIG treatment for KD patients who develop CA aneurysm. In that study, 27% of the patients had suspected incomplete KD and were eligible for algorithm application. They all would have IVIG treatment at presentation. In our patient cohort, there were 33 cases in whom KD diagnosis was definite. When we checked how the aforementioned criteria performed in our patients with definite KD, 19 of 29 patients had at least three supplemental laboratory criteria. Thus, the sensitivity of AHA criteria in our patient cohort was 65.5%.

The majority of KD patients were diagnosed between the ages of 1 to 4 years[17]. Although less prevalent at other ages, children as young as one month and adults in their second decades have also been reported[1]. Although the conventional diagnostic criteria are very useful for diagnosis, it should be noted that KD at less than one year of age is associated with higher incidence of atypical presentation and CA involvement, making the diagnosis challenging[18]. In order to overcome this, the contribution of specific laboratory criteria is very important. In our patient cohort, there was only one patient less than six months of age. Among the 24 KD patients reported by Özdemir et al.[19], four were less than one year of age. However, in our series, more than one-fourth of patients (9 patients) were less than one year of age. When supplemental criteria were applied for this age group, seven of nine patients had more than three laboratory criteria (sensitivity 77.7%). Thus, the criteria performed well in this group of patients.

Vasculitides tend to have different features in different countries and groups. Kawasaki disease -like other vasculitides- also has different features. Although this is a single-center series, we believe the data reflect the characteristics of our population since our institute is the main referral center for the major portion of the country. The timing of certain features of KD in this report showed some differences from those reported previously. We believe that it is important to report these differences for the strategic planning of future genomic studies.

REFERENCES

1. Newburger JW, Takahashi M, Gerber MA, et al. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004; 114: 1707-1733.
2. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children (Japanese). Jpn J Allergy 1967; 16: 178-222.
3. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. J Pediatr 1991; 119: 279-282.
4. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1993; 87: 1776-1780.
5. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984; 2: 1055-1058.
6. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986; 315: 341-347.
7. Anderson MS, Todd JK, Glode MP. Delayed diagnosis of Kawasaki syndrome: an analysis of the problem. Pediatrics 2005; 115: e428-433.
8. Ozen S, Bakkaloğlu A, Düşünsel R, et al. Childhood vasculitides in Turkey: a nationwide survey. Clin Rheumatol 2007; 26: 196-200.

9. Karageorgaki ZT, Bertsias GK, Mavragani CP, et al. Takayasu's arteritis: epidemiological, clinical and immunogenetic features in Greece. Clin Exp Rheumatol 2009; 27: s33-39.

10. Koné-Paut I, Yurdakul S, Bahabri SA, et al. Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. J Pediatr 1998; 132: 721-725.

11. Michie C, Kinsler V, Tulloh R, Davidson S. Recurrent skin peeling following Kawasaki disease. Arch Dis Child 2000; 83: 353-355.

12. Scott JS, Ettedgui JA, Neches WH. Cost-effective use of echocardiography in children with Kawasaki disease. Pediatrics 1999; 104: e57.

13. Erdoğan I, Çeliker A, Ozkutlu S, Ozer S, Alehan D, Karagöz T. Assessment and follow-up of coronary abnormalities in Turkish children with Kawasaki disease. Anadolu Kardiyol Derg 2009; 9: 342-344.

14. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 2003; 112: 495-501.

15. Harnden A, Takahashi M, Burgner D. Kawasaki disease. BMJ 2009; 338: 1133-1138.

16. Yellen ES, Gauvreau K, Takahashi M, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. Pediatrics 2010; 125: e234-241.

17. Manlhiot C,Yeung R, Clarizia N,Chahal N, McCrindle BW. Kawasaki disease at the extremes of the age spectrum. Pediatrics 2009; 124: e410-415.

18. Tseng CF, Fu YC, Fu LS, Betau H, Chi CS. Clinical spectrum of Kawasaki disease in infants. Zhonghua Yi Xue Za Zhi (Taipei) 2001; 64: 168-173.

19. Özdemir H, Çiftçi E, Tapısız A, et al. Clinical and epidemiological characteristics of children with Kawasaki disease in Turkey. J Trop Pediatr 2010; 56: 260-262.