Kawasaki Disease: A University Hospital Experience

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ABSTRACT

Background: Kawasaki disease (KD) is an acute vasculitis of unknown etiology; it is the leading cause of acquired heart disease in children. KD is poorly understood in the Kingdom of Saudi Arabia (KSA).

Objective: To examine the epidemiological, clinical characteristics, and outcomes of KD in children diagnosed and treated at a tertiary care hospital in eastern province of the KSA.

Materials and Methods: A retrospective study of 35 patients admitted to the hospital with the diagnosis of KD was conducted at King Fahd Hospital of the University, Al-Khobar, KSA, from 1992 to 2012. Demographics, clinical features, laboratory findings, treatment, and patient outcome were analyzed.

Results: The incidence was 7.4 per 100,000 children under five. The male-to-female ratio was 1.9:1. The median age at diagnosis was 15 months, and the diagnosis was made after a mean of 8.1 days of fever. A seasonal peak during the winter-spring months was observed. Thirty-two patients (91%) had classical presentation of KD. Conjunctivitis, changes in the oropharynx, and a polymorphous rash were the most common manifestations. Cardiac involvement was detected in 51%, with coronary artery abnormalities (CAA) noted in 34%. Patients were treated with immunoglobulin and aspirin. The CAA regressed in all patients but one by 12 months. This one child still had persistent aneurysms at 2 years of follow-up.

Conclusion: The findings of this study showed that the basic clinical and epidemiological features associated with KD, in the KSA, were similar to those reported from regions in other parts of the world. A nationwide survey, however, is necessary to investigate the overall incidence, potential risk factors, and magnitude of KD disease in the KSA.

Key words: Coronary aneurysm, Kawasaki disease, Saudi Arabia

INTRODUCTION

Kawasaki disease (KD) is an acute multisystem vasculitis of the small and medium caliber vessels, with a striking predilection for the coronary arteries.[1] Since its original description by Tomisaku Kawasaki in 1967, KD has emerged as a leading cause of acquired heart disease in children.[2,3] KD is recognized worldwide among different ethnic groups.[4,5] Most patients are children below five years of age. Males slightly predominate by a ratio of 1.5-2:1.[6] Despite mounting evidence of the possible role of microbiological agents, the etiology of KD remains obscure.[1,7] The diagnosis of KD is based primarily on clinical criteria that correspond to clinical symptoms.[8,9] Early recognition of KD is crucial for patient management and the prevention of long-term sequelae. Treatment with intravenous immunoglobulin (IVIG) and aspirin reduces the risk of coronary artery abnormalities (CAA) when administered within 10 days of fever onset.[8,10] Although
many studies have reported on this disease, studies from Saudi Arabia and the region are scarce.[11-13] In the current report, the epidemiology and clinical profile of 35 patients with KD, seen over a 20 year period at King Fahd Hospital of the University, Al-Khobar, in the eastern province of Saudi Arabia, are presented.

MATERIALS AND METHODS

The medical records of all patients that had KD between October 1992 and September 2012 were retrieved and retrospectively analyzed. The diagnosis of KD was based on the diagnostic guidelines reported by the American Heart Association Committee on Rheumatic Fever, Endocarditis, and KD.[8] Fever persisting for at least 5 days and the presence of at least four of the following five principal features:
1. Changes in extremities: Acute: Erythema or edema of hands or feet Convalescent: Desquamation of fingertips
2. Polymorphous exanthem
3. Bilateral, bulbar conjunctival injection without exudate
4. Changes in lips and oral cavity: Erythema and cracking of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral.

Incomplete KD was defined as:[8]
Fever lasting for at least 5 days and
1. At least two of the five clinical criteria for KD
2. Absence of any other reasonable explanation for the illness
3. Laboratory findings consistent with severe systemic inflammation.

The diagnosis of KD can be made on day four of illness in the presence of four or more criteria.[8] Demographic data (age at presentation, gender, and ethnicity), clinical features (symptoms at presentation, fever duration, comorbidity, treatment with IVIG, and aspirin), laboratory data (complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function testing, urine analysis, cerebrospinal fluid (CSF) analysis, and abdominal ultrasound) were collected and reviewed. Twelve lead electrocardiogram (EKG) and two-dimensional echocardiography were performed for evaluation of the structures and the function of the heart in all children on presentation, 2 weeks after the diagnosis and thereafter depending on the initial findings. Continuous variables (such as age) were expressed as the mean, median, and range. Absolute numbers as well as percentages are presented for the study variables. As this is a descriptive study, no statistical tests of significance were used.

RESULTS

During the study period, the total number of children (≤12 years old) admitted to the pediatric ward was 24,402. Thirty-five patients were diagnosed with KD, for an incidence of 7.4/100,000 children younger than 5 years of age. As to ethnicity, 25 (71.4%) patients were of Saudi descent, 7 (20%) Middle Eastern, and 3 (8.6%) Asian. There were 23 males and 12 females, with a male to female ratio of 1.9:1. The mean age at diagnosis was 25.5 months and the median was 15 months (range 6 weeks to 8 years). Twelve (34.3%) children were diagnosed at less than 1 year of age, and 31 (89%) at less than 5 years of age. The disease occurred during the winter season in 16 cases (45.8%), spring in 12 (34.3%), summer in 4 (11.4%), and fall in 3 (8.5%) [Table 1]. The diagnostic criteria for KD were fulfilled in 32 (91.4%) patients. Only three (8.6%) cases were diagnosed with incomplete criteria (two patients with a positive echocardiogram and one after exclusion of other possible diagnoses).

| Table 1: Demographic and epidemiological data of 35 patients with Kawasaki disease |
|---------------------------------|-----------------|
| Age at presentation             | (6 weeks-8 years) |
| Mean                            | 25.5 months     |
| Median                          | 15 months       |
| Gender (%)                      |                 |
| Male                            | 23 (66)         |
| Female                          | 12 (34)         |
| Male:female                     | 1.9:1           |
| Ethnicity (%)                   |                 |
| Saudi                           | 25 (71)         |
| Middle Eastern                  | 7 (20)          |
| Asians                          | 3 (9)           |
| Age distribution (years) (%)    |                 |
| ≤1 year                         | 12 (34)         |
| >1 to ≤5 years                  | 19 (54)         |
| >5                              | 4 (11)          |
| Season pattern (%)              |                 |
| Winter                          | 16 (45.8)       |
| Spring                          | 12 (34.3)       |
| Summer                          | 4 (11.4)        |
| Autumn                          | 3 (8.5)         |
Five (14%) patients with four or more criteria were diagnosed at 4 days of fever. The mean duration of fever was 8.1 days (range 4-21), with five (14%) patients having fever for less than 5 days and eight (23%) patients having fever for more than 10 days, at diagnosis. The frequency of KD criteria among the patients is as follows [Table 2]: Conjunctivitis and oropharyngeal changes 91.4% each, skin rash 85%, cervical lymphadenopathy 71%, and changes noted in the peripheral extremities 66%. The associated clinical features included irritability, arthralgia, gastrointestinal symptoms, jaundice, anemia, perineal desquamation, hydrops of the gallbladder, and aseptic meningitis [Table 2].

The Laboratory data are summarized in Table 3. Anemia for age was detected in 66% of cases, leukocytosis in 63% and thrombocytosis (either on presentation, or toward the end of the second week of the illness) in 86%. All cases except two had an increased ESR (range 16 to 152 mm 1st hour); similarly, all but one had increased CRP levels. Elevated serum transaminases were found in 28% of cases, a reduced albumin level in 80%, and increased serum bilirubin level in 24%. The CSF was analyzed in 7/35 cases and pleocytosis was detected in 4 of them. Abdominal ultrasound was performed in 18/35 children. Only one of these patients had hydrops of the gallbladder. The EKG showed sinus tachycardia in 17/35 (49%) patients, a depressed ST segment in 1, and reduced QRS voltage in 1 child. Cardiac involvement was found in 18/35 (51%) children (12 males and 6 females). CAA were detected in 12/35 (34%) patients, 6 had ectasia, and 6 had aneurysms. The right coronary artery was involved in four patients, in two the left coronary artery was involved, and in six patients, both the right and the left coronary arteries were involved. The aneurysms varied in size; four patients had small aneurysms (<5 mm) and two had moderate sized aneurysms (<8 mm). A minimal to moderate pericardial effusion was seen in nine cases and valvular regurgitation (mitral and tricuspid valve) in five. Left ventricular function was within normal limits in all cases [Table 4]. Regression of the coronary lesions was observed in all but one at 12 months of follow up. This patient had persistent coronary artery aneurysms at 2 years of follow up. All other cardiac abnormalities have resolved completely on follow-up. Aspirin (80-100 mg/kg/day) was given to all children during the acute phase, followed by 3-5 mg/kg/day for patients with CAA. IVIG (2 g/kg over 12 hours or 400 mg/kg/for five consecutive days) was administered in all cases. Sixty-nine percent of the cases received IVIG within 10 days of the onset of fever. The rest of the patients (51%) received IVIG after the 10th day of illness. Two patients, that had persistent fever 48 hours after the initial IVIG dose, received a second dose.
DISCUSSION

KD in an eastern province of Saudi Arabia is primarily a disorder affecting pre-school children. The incidence was 7.4 per 100,000 children under 5 years of age in this study; this is comparable to the rate previously reported from the region and from other countries. However, the incidence was lower than that reported from far eastern countries. The worldwide annual incidence of KD derived from a nationwide epidemiological survey and from analysis of hospital based data varies widely from 3.4 to 218.6/100,000 children less than 5 years of age. The true incidence in most Middle Eastern countries is not known. The recently published data from Jordan reported an incidence rate of 0.09%. The age distribution and male preponderance observed in this study is consistent with other reports from the region and various parts of the world. The disease occurred throughout the year, with seasonal clustering observed during the winter and spring months. This finding is consistent with the results of other major epidemiological studies conducted in different countries.

The diagnosis of KD is based on well-established clinical criteria. In this review, 32 (91%) children had classic disease and only 3 had incomplete disease. It has been postulated that children with incomplete disease are at higher risk of developing CAA than those with classical presentations. Thus, KD should be part of the differential diagnosis, particularly in younger children with fever and less than four criteria that have suggestive laboratory findings such as an increased white blood cell count (WBC), ESR, CRP, or thrombocytosis after 7 days of fever. In this study, the mean duration of fever at diagnosis was 8.1 days. Seventy-eight percent of the cases had been diagnosed within 10 days after the onset of fever. Although this finding may suggest a better awareness of KD, among health care workers, over one-quarter of the patients had their disease diagnosed after 10 days of fever. Delay in the diagnosis and management of KD carries a significant risk for developing CAA. Anderson et al noted that delayed diagnosis was not significantly related to healthcare system factors but was related to the dispersion over time of the development of clinical features.

The clinical findings essential for the diagnosis of KD together with the associated clinical and laboratory findings were used for the diagnosis of KD in all patients. The frequency of the principal clinical criteria observed in this study was in accordance with the results of other studies.

Cardiac involvement is the most important feature of KD; it has been variably reported in up to 50% of cases. In untreated KD, 20-40% of patients develop CAA. Timely treatment with IVIG, however, decreases the incidence of coronary artery disease to less than 5%. Among the children in the current series, 18/35 (51%) had cardiac involvement. Pericardial effusion occurred in 8 (22%) cases. The effusion was minimal and transient in most. One patient (a 5 year old girl), developed a significant pericardial and pleural effusion, respiratory distress, and hypotension. She required pericardiocentesis and respiratory support, before she made a full recovery.

Another non-coronary cardiac involvement was valvular regurgitation, which was observed in 14% of cases. The mitral and tricuspid valves were affected in three patients and the mitral valve alone in two; the regurgitation was mild and resolved within a few months of follow up. This is consistent with studies reported previously. In the current study, the incidence of CAA was high, with 12 patients (37%) developing coronary changes despite treatment with IVIG. This might be explained by a delay of recognition of the disease, and hence a delay in starting treatment. As well as a younger age, since 50% of these groups were infants, and less than 1 year of age. A young age (age < 1 year), male gender, and prolonged fever are known risk factors for developing coronary abnormalities, which may precipitate thrombosis or evolve into segmental stenosis during the chronic phase of disease. Coronary artery involvement regressed in all patients but one by 12 months. This patient had persistent coronary lesions at 2 years of follow-up. Small and medium sized aneurysms are known to have a greater likelihood of regression.

CONCLUSION

The findings of this study document the incidence of Kawasaki disease in this region of the KSA and confirm the clinical similarities with various reports from other parts of the world. Early diagnosis and prompt treatment are crucial in preventing serious complications. A prospective study at the national level is necessary to investigate the overall incidence and magnitude of Kawasaki disease in the Kingdom of Saudi Arabia.
REFERENCES