Pattern of clinical features of Kawasaki Disease

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ABSTRACT

Objectives: To study the pattern of clinical features, complications, and outcome of Kawasaki disease among Saudi children.

Methods: Medical records and referral letters of all children (1997 through to 2001) diagnosed with Kawasaki disease were reviewed. This study was carried out at King Faisal Specialist Hospital and Reserch Center, Riyadh, Kingdom of Saudi Arabia. Collected data included clinical features, laboratory results, echocardiogram findings, therapy, complications and outcome.

Results: Thirteen children (10 boys, 3 girls) were reviewed, age range from 0.3 to 7 years (mean 3.4 years). Nine patients met 5 out of 6 criteria for the diagnoses of Kawasaki disease and 4 met 4 out of 6 criteria and coronary aneurysm. Thirteen patients had fever and skin rash for more than 5 days, 12 had extremity and oral mucus changes, 9 had bilateral conjunctivitis, and 7 had cervical lymphnode enlargement. Other associated clinical features include diarrhea, and aseptic meningitis in 3 patients, ischemia of the fingers and toes in 2, arthritis in 2, arthralgia in one, seizure and pneumonia in one. Hepatosplenomegaly, pancytopenia and elevated liver enzymes in one, hepatomegaly and normal liver enzymes in 2 patients. Cardiac complication seen in 4 patients (30%), all of them were boys, 3 had coronary artery aneurysm (4-7 mm) and one had giant aneurysm (9mm), one of the 3 patients had axillary and subclavian artery aneurysm as well. Two out 4 patients were treated with intravenous immunoglobulin and aspirin within 10 days of illness and one was treated on day 21 and one was treated with aspirin alone. Aneurysmal changes persisted in 3 patients and resolved in one patient who was treated early. Extra-cardiac complications include reaction to intravenous immunoglobulin, coagulopathy, thrombocytopenia, hemophagocytic syndrome and ischemia of peripheral extremities.

Conclusion: Our observation showed a high percentage (30%) of coronary aneurysm and unusual complications, this is most likely due to delay in the diagnosis and initiation of treatment.

Keywords: Kawasaki disease, coronary artery aneurysm, immunoglobulin.

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Kawasaki disease (KD) an acute multisystem vasculitis, initially described as mucocutaneous lymph node syndrome,[1] occurs predominantly in infants and children. The exact etiology remains unknown, however, recent studies support the ideas that it may be triggered by activation of immunocytes stimulated by bacterial toxins or superantigens, leading to increased levels of cytokines and activation of an arachidonic acid cascade.[2-5] These inflammatory reactions result in diffuse vasculitis and subsequently development of acute clinical symptoms and cardiovascular complications. The diagnosis of KD requires the presence of 5 out of the 6 clinical criteria which were described in English literature and accepted worldwide.[6] The administration of a high dose of intravenous immuno globulin (IVIG) and acetyl salicylic acid (ASA) decreases the prevalence of coronary artery

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abnormalities and improves acute clinical manifestations.[7,8] We evaluate the pattern of clinical features and the complications in 13 Saudi patients with KD who were referred to our tertiary medical center, due to unusual presentation, complications and lack of treatment, or both.

Methods. All patients diagnosed with KD were identified from a database at King Faisal Specialist Hospital & Research Centre in the Department of Pediatrics, Section of Rheumatology, from November 1997 through to March 2001. All available out-patient clinic and in-patient medical records were reviewed for each case. Collected data included age at presentation, gender, duration of illnesses at the time of KD diagnosis, clinical presentation, laboratory results, echocardiography finding, timing, duration, choice of medications, complications and outcome. Patients were diagnosed and included according to KD criteria; 8 were treated with standard protocol.[7] Patients who had coronary artery abnormalities after a prolonged fever but did not have at least 4 clinical features of the KD criteria, or have alternative diagnosis both together with KD also were included.

Results. Thirteen patients were enrolled in this study, 11 of whom had inpatient and outpatient medical records available for review and referral letters. Out-patient medical records for 2 patients were reviewed. There were 10 boys and 3 girls, with ages ranging from 0.3 to 7 years (mean 3.4 years). All our group of patients was Saudi nationals. The frequencies of classic clinical features of KD and other symptoms prominent among the patients are listed in **Table 1.** Eight (61.5%) of 13 patients met all of 5 clinical criteria, and 4 (30%) met the minimum requirement of 4 criteria. A 10-month-old boy who was referred with cardiac infarction and a large coronary artery aneurysm diagnosed as KD at a referral hospital 4 months prior to this presentation was also included in this study group. Many other symptoms were common among our study group of patients with acute KD. Predominant upper respiratory tract infection including sore throat in all 13 patients. Patients with seizure had abnormal electroretinogram and with pneumonia had radiological evidence of pneumonitis. Hepatosplenomegaly, pancytopenia, and abnormal liver enzymes and function were observed in one patient who underwent liver biopsy and bone marrow examination and subsequently diagnosed as hemophagocytic syndrome and received treatment accordingly. Two patients had hepatomegaly with normal liver function. One patient presented with cyanosis and ischemia of the fingers and toes in the acute febrile illness that improved with treatment. These features had been reported before.[9]

Table 1 - Characteristic clinical manifestation in patients with acute Kawasaki disease.

Classical clinical features of KD	**N of patients (%)**
Fever > 5 days	13 (100)
Rash	13 (100)
Extremity changes	12 (92)
Oral changes	12 (92)
Conjunctivitis	9 (69)
Cervical node enlargement	7 (54)
Associated other clinical features	**N of patients (%)**
Sore throat	3 (25)
Meningeal signs	3 (25)
Diarrhea	3 (25)
Peeling of fingers	3 (25)
Arthritis/Arthralgia	3 (25)
Ischemia of finger/toes	2 (16.7)
Vomiting	2 (16.7)
Seizure	1 (8.3)
Pneumonitis	1 (8.3)

KD - Kawasaki disease, N - number

Extra-cardiac complications observed in our study group of patients included reaction to IVIG in 2, coagulopathy in one, throat swab culture positive for group B streptococcus (GBS) in one, and thrombocytosis in 4. Coronary artery aneurysm (CAA) was detected by echocardiography in 2 (15%) of 13 patients at the time of diagnosis and in 2 (15%) during convalescent period, all were boys. One boy had a giant CAA that was measured 9mm internal diameter, one boy had diffuse dilatation of CAA measured 5 mm internal diameter as well as axillaries and subclavian artery involvement causing aneurysmal dilatation. One boy had CAA, detected during convalescent period measured 5-7 mm in left coronary artery (LCA) and 4-6mm in right coronary (RCA), and extended during follow up to involve distal part of both CA. One boy who had CAA at the time of diagnosis showed normal size of coronary arteries on subsequent follow up echocardiography examination. Two of the 4 boys had been treated with high-dose IVIG (2 gm/kg/dose) and aspirin (100 mg/kg/day) before the 10th day of illness (day 7 and 9) and one boy had been treated on day 21 of the illness. All these 3 boys received 2 doses of IVIG

with persistent fever and 3 doses of intravenous methylprednisone 30 mg/kg/day for 3 consecutive days when fever did not resolve. One patient who was referred with cardiac infarction 4 months after diagnosis of KD did not receive IVIG and was treated with aspirin alone. Among 2 patients treated within 10 days of diagnosing KD, CAA persisted in one and in the other CAA developed during convalescent period and progressed to involve the axillary and subclavian arteries. One boy who was treated on day 21, CAA resolved later.

The interval period from onset of fever to diagnosis and treatment of acute KD ranged from 5 to 21 days (mean 8 days). Eight of 13 patients received IVIG or ASA on or before the 10th day of their illness. Two patients treated with naproxen and or ASA alone, one of the 2 was not diagnosed as KD and treated for frank arthritis, the other patient did not receive IVIG and the reason was unclear.

All patients underwent thorough investigations for infection including septic work up (blood, urine, stool, and throat swab culture) and 2 patients had CSF examination. All received antibiotics before the diagnosis of KD was made. Patient who received naproxen had a bone marrow examination as part of the evaluation for fever of an unknown origin. Nine patients were treated with single antibiotic, either amoxicillin or a cephalosporin, 3 patients were treated with 2 or more antibiotics, oral or parenteral or both. One of the 3 received 2 courses of antibiotics including intravenous cephalosporin and aminoglycoside, before and after the diagnosis of KD and later diagnosed as having hemophagocytic syndrome complicating KD and treated with intravenous etoposide in addition to steroids with a good response.

Discussion. Kawasaki disease had been recognized worldwide.[1] All our patients were treated for infection with antibiotics and the diagnosis of KD was made either in this center or when the physician noticed peeling of the skin or thrombocytosis or both during acute febrile illness. The possible explanation in our experience for the delay in diagnosis of KD and treatment may be related to the orientation of treating physician by additional signs and symptoms less commonly associated with KD (such as vomiting, diarrhea, sore throat, and joint pain associated with fever) and lack of awareness that KD disease can present with clinical features other than the classical diagnostic criteria. Most of our group of patients met the known diagnostic criteria for KD,[6] and responded to the standard treatment provided to them in the acute febrile illness and returned back to their normal healthy condition. Since infectious illnesses were common in our society, many clinical features including sore throat, otitis media (symptoms of upper respiratory tract infection), vomiting, diarrhea, irritability associated with fever considered as infection and interestingly these features were common in our group of patients, particularly among infants and young children. Our entire group of patients underwent thorough extensive laboratory investigations before the diagnosis of KD was made and in 2 patients bone marrow examination was performed. The most common diagnostic tests included complete blood count, erythrocyte sedimentation rate, urea, electrolytes, creatinin, cultures for blood, urine and throat swab, serology for common viruses, salmonella and anti-streptolysin titer and anti-nuclear antibody, as well as all other reasonable diagnostic test required for evaluation of prolonged acute febrile illnesses.

A study from Japan suggested that treatment with IVIG in infants and young children is effective in preventing the development of CAA.[10] The study from North America also suggested that treatment of KD with single high dose of IVIG (2 gm/kg/d) and ASA (100 mg/kg) in 3 to 4 divided doses is effective in resolving acute febrile illness and preventing CAA,[8] especially if treatment is introduced to the patients within 10 days of diagnosing KD. Out of nine of the 13 patients treated with standard protocol, only one patient developed CAA, and the remaining 8 patients had no cardiac complication. Extreme age, male infant carry a high risk of cardiac complication,[11] and this observation was true in our 4-month-old boy who was treated on day 7 of febrile illness according to standard protocol without response, required 2nd dose of IVIG and fever persisted.[12] Intravenous methylprednisone infusion (30 mg/kg/d) for 3 consecutive days according to previous experience[13] was given when he did not respond to 2 doses of IVIG, and the fever subsided after steroid treatment, yet he developed significant CAA. Also another 6-month-old boy who was treated with ASA alone developed CAA with significant morbidity, while 2 other patients 6 years and a 10-month-old treated on day 14 and 10 of febrile illness had no cardiac complications. From these observations we are unable to conclude that infants are at higher risks than young children for developing CAA as complications of KD. Younger age and prolonged febrile illness may be an independent risk factor for development of coronary aneurysms in KD.[11] Primary caregivers must be aware of the occurrence of KD in all age groups particularly in infant and children.

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