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Clinical Experience of Kawasaki Disease in Two Tertiary Care Centers in Jeddah, Saudi Arabia

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Abstract. To analyze the clinical presentation, investigations, diagnosis and management of patients with Kawasaki disease seen at the two centers, an analytic study of data from the medical records of all patients of Kawasaki disease admitted to King Abdulaziz University Hospital and King Faisal Specialist Hospital and Research Centerwas done from January 2000 to June 2012. A total of 56 patients were included in the study with the mean age of 30.5 months (range from 2-132 months). Diagnosis and administration of intravenous immunoglobulin were performed after the mean of 8.4 days (ranged from 3-31 days). Twenty-eight patients had classical Kawasaki disease (50%) while the other 28 had incomplete Kawasaki disease (50%). A wide variety of clinical symptoms and signs were found in our patients. Thrombocytosis was detected in 32 patients at presentation. Coronary artery lesion was detected in 27 patients; 13 from classical Kawasaki disease group and 14 from incomplete Kawasaki disease group. Out of these, 20 had thrombocytosis at presentation, making it a significant risk factor for the development of coronary artery lesion (p-value = 0.013). The percentage of incomplete Kawasaki disease is quite high in our patients. Epidemiological studies are needed, and National Kawasaki Disease Awareness Program, aiming at avoiding delays in diagnoses, is suggested.

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Introduction

Kawasaki disease (KD) initially called Acute Febrile Mucocutaneous Syndrome, described in 1967 by Tomisaku Kawasaki in Japan[1], is considered as one of the most common vasculitides in infants and children. The etiology of the KD is unknown. There are recent studies which support the idea of superantigens, which activates the T-cell inflammatory processes and cause diffuse vasculitis with the acute and sub-acute clinical manifestations and cardiac complication of KD[2]. The clinical features of Kawasaki disease are insidious which makes it difficult to diagnose, and it is associated with high morbidity and mortality if untreated[3-5].

Although the incidence of KD varies worldwide, its highest prevalence is among the Asian countries, especially in Japan with an incidence rate of 216.9 / 100.000 in children below 5 years of age, and its lowest occurrence is in European populations[6]. However, due to paucity of literature of KD in Saudi Arabia[7], the author aimed to describe his experience with KD.

Methodology

Data was collected from the medical records of all pediatric patients admitted to King Abdulaziz University Hospital (KAUH) and King Faisal Specialist Hospital & Research Center (KFSH&RC), for the period of January 2000 - June 2012 and diagnosed as KD based on the recent American Heart Association Guidelines.

Clinical symptoms and signs, laboratory results, echocardiogram reports at the time of diagnosis and at the follow up six weeks after discharge, radiological tests (chest x-ray and abdominal ultrasound) and details of medications were collected from the patients' charts. The patients were grouped according to their age and duration of fever. Age groups were as follows: Group A less than 12 months old, Group B age between 12-60 months, and Group C older than 60 months. As for the fever, groups were as follow: Group 1 fever duration less than 5 days,

Group 2 fever duration between 5-10 days, and Group 3 fever duration more than 10 days.

The diagnosis of Kawasaki disease was based on the revised AHA 2004 guidelines which are an unexplained fever (> 37.5°C) that lasts for five days or more with at least four out of five from the following: 1) Bilateral non purulent conjunctivitis; 2) Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue; 3) Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase); 4) Polymorphous rash; 5) Cervical lymphadenopathy (at least one lymph node > 1.5 cm in diameter). Patients who did not fulfill the criteria were diagnosed as incomplete KD. Coronary artery lesion (CAL) was defined as an abnormality in any of the coronary arteries ranging from ectasia to giant aneurysm[8]. Leukocytosis was defined as white blood cell (WBC) $\geq$ 14 (10^3/ml), anemia as hemoglobin (Hgb) $\leq$ 12 g/dl. Platelet counts were divided into three groups: Thrombocytopenia with counts < 150 X 10^3/ml, platelet with normal range 150 – 400 X 10^3/ml and thrombocytosis > 400 X 10^3/ml.

The research has the approval of Biomedical Ethical Committees of both centers. Descriptive studies were done using Statistical Package for the Social Sciences (SPSS) Version 17. Chi square was done to determine the relationship and differences between the proportions. Data were presented as frequencies (Percentage). A P-value < 0.05 was considered statistically significant.

Results

A total of 56 patients enrolled in the study, 31 patients from KAUH and 25 patients from KFSH&RC. The mean age of the patients is 30.5 months (range from 2-132 months). Seventeen (30.4%) patients were younger than 12 months (Group A) while 34 (60.7%) patients were aged between 12-60 months (Group B), and 5 patients were older than 60 months (Group C). Thirty-three (58.9%) patients were male while 23 (41.1%) were female. The mean febrile days in our population is 8.4 days (range 1-30 days). Nine (16.1%) patients had febrile days less than 5 days (Group 1). Thirty-eight (67.9%) patients had febrile days between 5-10 days (Group 2) while 9 (16.1%) children had fever more than 10

days (Group 3). The clinical signs and associated symptoms in the patients are shown in Table 1.

Table 1. Kawasaki disease, oral changes including strawberry tongue, cracked lip, erythematous lips, extremity changes including erythema, swelling, desquamation of the skin.

Common Signs Detected	Number of Patients (%)
Fever	56 (100%)
Rash	46 (82.1%)
Oral Changes	44 (78.6%)
Conjunctivitis	40 (71.4%)
Extremity Changes	31 (55.4%)
Cervical Lymph Adenopathy	29 (51.8%)

Less Common Associations	Number of Patients (%)
Vomiting	18 (32.14%)
Diarrhea	17 (30.36%)
Upper Respiratory Tract Infection	12 (21.42%)
Congested Throat	5 (8.93%)
Joint Pain & Arthralgia	3 (5.36%)
Meningeal Signs	1 (1.8%)
Pleural Effusion	1 (1.8%)
Anterior Uveitis	1 (1.8%)
Gallbladder Hydrops	1 (1.8%)

Leukocytosis was found in 35 (62.5%) patients, anemia was present in 38 (67.9%) patients and thrombocytosis was found in 32 (57.1%) patients. Mean WBC was 11.5 X 10^3/ml with range of (4.8-43 X 10^3/ml). The mean of Hgb is 10.2 g/dl with a range of (7-14.1 g/dl) and the mean of platelets is 547 X 10^3/ml with range of (133-1510 X 10^3/ml).

Half of the patients were classified as classical KD while the other half had incomplete KD. CAL was found in 27 (48.2%) patients. 13 (48.1%) of CAL positive patients were from classical Kawasaki disease group while 14 (51.8%) patients had incomplete Kawasaki disease (p-value = 0.78). CAL was found in 19 (70.1%) patients from group (B), 7 (25.9%) from group (A) and one (3.7%) patient from group (C) with p-value = 0.25. CAL was high in the fever Group 2 with patient number of 21 (77.7%), n=4 (14.8%) in Group 3 while the lowest was in group (1)

n=2 (7.4%) with p-value = 0.19. Out of 27 patients with CAL, 20 had thrombocytosis and only seven had values < 400 X 10^3/ml. Twelve patients with thrombocytosis did not develop CAL.

No relationship of significance was found between CAL and the gender (p-value = 0.25) as well as with the clinical symptoms. The only statistically significant relationship between CAL and laboratory tests in the study was with thrombocytosis with p-value = 0.013.

Discussion

Although the incidence (per 100,000 children below the age of 5 years) of KD is maximum in Japan (218.6) followed by its neighbors, namely South Korea, Taiwan and China (113, 64 and 55, respectively), the global presence of the disease is a known fact[9-11]. Incidence in USA is around 19, slightly less than in Canada while European countries have a much less incidence, usually below 10[12-14]. No epidemiological study has been done in KSA, but all tertiary care hospitals are diagnosing and treating the condition for more than two decades. This is evident from the study. Exact incidence is not known in other countries of the Middle East, as well as in India and Pakistan. However, the number of cases reported or published and the data on the diseases, which are common in the community is indicative of the fact that incidence of KD is relatively much less than in Middle East countries and its neighbors as compared to countries in East Asia[15,16]. Epidemiological studies are needed in KSA and its neighbors in order to have the exact data, which can confirm this common observation.

Based on this big variation in incidence of KD among Asian countries, the use of the phrase 'of Asian origin', which is used extensively even by text books[17], should be replaced by the phrase 'of East Asian origin' while describing the much higher incidence of KD among children originating from Japan and its neighbors. Symptomatology in our patients is similar in type and frequency to most of the studies on KD from other parts of the world, but the percentage of incomplete KD (50%) in the study is much more than the other studies[18-20]. The criteria for diagnosis of KD are only partially met in these patients. The study failed to show any significant difference in gender (P-value 0.25) although a significant dominance of male children is known and proved in most of the studies[21].

The presence of CAL in 27 (48.2%) patients is also higher as compared to other studies[22]. It may be related to a delay in initiation of immunoglobulin due to a delay in diagnosis (range 3-31days).

Delay in diagnosis is attributed to the fact that half of the total patients had incomplete KD. This means that they only had few of the cardinal symptoms of KD rendering them difficult to diagnose[23]. Moreover, out of this group of incomplete KD, only 50% had CAL which would have further impeded the process of reaching an early diagnosis. Studies have shown the importance of echocardiogram in early detection of CAL to facilitate early diagnosis and treatment[24].

Known risk factors related to the development of CAL (prolonged fever, anemia, high leukocyte counts, high band counts, C-reactive protein and male gender)[25-27] were not found significant in our patients. Thrombocytopenia at presentation is a known risk factor in development of CAL[28], but contrary to this, the only statistically significant risk factor related to CAL in our patients was thrombocytosis. This might again be related to delay in the referral, diagnosis and initiation of treatment as both high platelet counts and higher incidence of CAL are found in later stages of KD[29,30].

Considering the presence of KD in the country, a National Kawasaki Disease Awareness Program is needed, which will help in enhancing the understanding and increasing the high index of suspicion of KD among general practitioners and pediatricians. This will directly help in the early detection of KD and the early initiation of treatment aimed at preventing the development of CAL and the subsequent complications related to it [31].

Conclusion

KD is being diagnosed and treated in tertiary care hospitals in KSA, thus, epidemiological studies are required for exact incidence. Thrombocytosis at presentation is a risk factor for the development of CAL. Percentage of incomplete KD is quite high in our patients and high index of suspicion is needed to avoid potentially harmful delays in diagnosis. A National KD awareness program is suggested. It is further suggested to international authors to use the term "of East Asian origin"

instead of using "of Asian origin" while describing higher incidence of KD in children living in or having origins in Japan and its neighbors.

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الخبرة السريرية لمرض كوازاكي في مركزين مرجعيين في جدة، المملكة العربية السعودية

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المستخلص. أجريت دراسة تحليلية للمرضى المصابين بداء كوازاكي والذين أدخلوا كلاً من مستشفى الملك عبدالعزيز الجامعي ومستشفى الملك فيصل التخصصي ومركز الأبحاث بجدة وذلك حتى يتسنى تحليل مظاهر وأعراض ذلك المرض وكذلك الفحوصات والتشخيص وأسلوب العلاج. أقيمت هذه الدراسة في الفترة ما بين يناير ويونيو ٢٠١٢ وشملت ٥٦ مريضًا تتراوح أعمارهم بين شهرين إلى ١٣٢ شهرًا، وكان المعدل العمري للمرضى هو ٣٠,٥ شهرًا. وكان معدل المدة التي سبقت التشخيص والعلاج بالغلوبولين المناعي الوريدي من نوع ج ٨,٤ يومًا حيث تراوحت من ٣ إلى ٣١ يومًا. ولقد وجد أن ٢٨ مريضًا مصابين بمرض كوازاكي الكلاسيكي (٥٠٪)، أما البقية (٥٠٪) فكانوا مصابين بمرض كوازاكي غير المكتمل. ولقد تنوعت الأعراض وعلامات المرض في المرضى الذين شملتهم الدراسة. وقد لوحظت زيادة في الصفائح الدموية لدى ٣٢ مريضًا. كما أن ٢٧ مريضًا كان لديهم إصابة في الشريان التاجي، ١٣ من مجموعة الكوازاكي الكلاسيكي وأربعة عشر من مجموعة الكوازاكي غير المكتمل. وقد وجد أن ٢٠ من هؤلاء كان لديهم زيادة في الصفائح الدموية ويمكن اعتبار ذلك عاملاً من عوامل الخطورة التي يؤدي إلى الإصابة بتلف الشريان التاجي. وكانت نسبة المصابين بالكوازاكي غير المكتمل كبيرةً في هذه الدراسة. وتوصي هذه الدراسة بعمل الإحصاءات ونشر الوعي عن مرض كوازاكي حتى يمكن تفادي التشخيص المتأخر للمرض.