

# Kawasaki disease in Western Saudi Arabia

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## ABSTRACT

**الأهداف:** إعطاء نبذة توضيحية عن مرض كاواساكي (Kawasaki disease) ونسبة حدوثه في المدينة المنورة بالمملكة العربية السعودية.

**الطريقة:** أُجريت هذه الدراسة الاسترجاعية في مستشفى الحمل والولادة بالمدينة المنورة، المملكة العربية السعودية وذلك خلال الفترة من يناير 2007م إلى يناير 2010م. لقد قمنا بمراجعة سجلات المرضى الذين أُشبهوا بإصابتهم بمرض كاواساكي وقد بلغ عددهم 51 مريضاً، ولقد أجازت اللجنة المنظمة للبحوث هذه الدراسة.

**النتائج:** أشارت نتائج الدراسة إلى ثبوت إصابة 24 حالة بمرض كاواساكي، ويبلغ متوسط أعمار المرضى عند التشخيص  $3.1 \pm 2.4$  عاماً. كانت أعمار غالبية المرضى أقل من 5 سنوات (83.3%)، وبلغت نسبة عدد الذكور إلى الإناث 1.7:1. تم تشخيص المرضى بعد  $8.1 \pm 3.3$  يوماً منذ بداية ارتفاع درجة الحرارة أي خلال المدة التي تتراوح ما بين 4-15 يوماً منذ بداية الحرارة، ولقد تم إعطاء المرضى بروتين الغلوبين المناعي عبر الوريد، فيما احتاج 2 من المرضى إلى جرعة أخرى من هذا العلاج. وتم فحص القلب بالموجات فوق الصوتية بعد  $10.1 \pm 3.9$  يوماً منذ بداية ارتفاع درجة الحرارة أي خلال المدة التي تتراوح ما بين 4-20 يوماً. وكانت مدة بقاء المريض في المستشفى  $7.9 \pm 5.8$  يوماً أي خلال المدة التي تتراوح ما بين 3-25 يوماً. لقد أصيب 3 مرضى باعتلال في شرايين القلب التاجية وكان عليهم القيام بعملية توسيع للشرايين التاجية في الموعد الأخير من المتابعة.

**خاتمة:** أشارت الدراسة إلى أنه يجب أخذ مرض كاواساكي بعين الاعتبار عند الشك بوجوده أياً من أعراضه من أجل التشخيص المبكر للمرض والوقاية من اعتلالات الشرايين التاجية، ونحن ننصح بعمل برنامج لتوعية الناس حول هذا المرض وأعراضه.

**Objectives:** To describe our experience on Kawasaki disease in the Madinah region, Kingdom of Saudi Arabia (KSA).

**Methods:** This is a retrospective hospital based study. The study was conducted in Maternity and Children Hospital, Madinah, Kingdom of Saudi Arabia during January 2007 to January 2010. The study included 51

patients' records as suspected cases of Kawasaki disease. The study was approved by the Ethical Committee.

**Results:** Twenty-four patients were proven to have Kawasaki disease in this study. The mean age of the patients at diagnosis was  $3.1 \pm 2.4$  years. Most patients were younger than 5 years (83.3%). The male to female ratio was 1.7:1. Diagnosis was made  $8.1 \pm 3.3$  days after start of fever with a range from 4-15 days. All patients received intravenous immunoglobulin (IVIG) with 2 requiring another dose of IVIG. Echocardiography was performed  $10.1 \pm 3.9$  days from onset of fever with a range of 4-20 days. The duration of hospital stay was  $7.9 \pm 5.8$  days with a range from 3-25 days. Three patients had coronary artery abnormalities and still have coronary artery dilatation at last follow-up appointment.

**Conclusion:** A high index of suspicion is mandatory for early diagnosis of Kawasaki disease as delayed diagnosis may lead to coronary lesions. A national awareness program on Kawasaki disease is recommended.

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Kawasaki disease is an acute febrile systemic vasculitis usually occurring in children younger than 5 years, and rarely reported in neonates and adults. It was first reported by the Japanese doctor Tomisaku Kawasaki in 1967.<sup>1</sup> The principal symptoms and findings include: 1. Fever persisting for 5 days or more. 2. Bilateral conjunctival congestion. 3. Changes of lips, and oral cavity: Redding of lips, strawberry tongue, diffuse injection of oral, and pharyngeal mucosa. 4. Polymorphous exanthema. 5. Changes of peripheral extremities: (acute phase): Redding of palms and soles,

Indurative edema: (convalescent phase): Membranous desquamation from fingertips. 6. Acute nonpurulent cervical lymphadenopathy. At least 5 items of the above 6 items should be satisfied for the diagnosis of Kawasaki disease. However, patients with 4 items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm, or dilatation is recognized by two-dimensional (2D) echocardiography, or coronary angiography.<sup>2</sup> The main complication of Kawasaki disease is coronary artery lesion that may result in myocardial infarction, or sudden death at a young age.<sup>3-5</sup> Coronary artery lesions develop in approximately 25% of untreated children. Early management with intravenous immunoglobulin (IVIG) and aspirin, decreases the incidence of coronary sequelae to approximately 10%.<sup>6-8</sup> Kawasaki disease is a worldwide disease but is commonly seen in the Japanese<sup>9</sup> and people from Asian countries.<sup>9</sup> Although Saudi Arabia is an Asian country, the situation of Kawasaki disease in patients is not documented due to paucity of the published data on this disease from the Kingdom of Saudi Arabia. The aim of this study is to describe our experience on Kawasaki disease in the Madinah region, Kingdom of Saudi Arabia.

**Methods.** This study is a retrospective hospital based study. It was carried out at the Maternity and Children Hospital, Madinah, Kingdom of Saudi Arabia. The work was approved by the Ethical Committee of the Hospital. During the 3-year study period from January 2007 to January 2010, we revised the medical records of all patients who were suspected to have Kawasaki disease and were sent to the cardiology clinic for echocardiography evaluation. Patients who fulfilled the clinical criteria for diagnosis of Kawasaki disease were included. The exclusion criteria included patients with proven diagnose other than Kawasaki disease, or patients who did not support the clinical criteria of the diagnosis of Kawasaki disease.

**Statistical analysis.** This study is a descriptive work, so no test for comparison was used. Continuous numerical data were tabulated, and expressed as mean  $\pm$  standard deviation. The Statistical Package for the Social Sciences (SPSS Inc., version 12, Chicago, IL, USA) was used for data analysis.

**Results.** During the study period, a total of 51 patients were sent for cardiac evaluation as suspected cases of Kawasaki disease. After completion of the process of diagnosis, only 24 patients were proven to have Kawasaki disease. The mean age of Kawasaki disease patients at diagnosis was  $3.1 \pm 2.4$  years, and they ranged from 0.3-8 years. Most of the patients were younger than 5 years (83.3%) and these included

5 patients less than one year. The male to female ratio was 15:9 (1.7:1). No recurrence was noted in any of the patients. All patients had fever for more than 5 days. In 2 patients, diagnosis was made on the fourth day of fever as patients had 4 clinical criteria by the fourth day. The rate of occurrence of the 5 main diagnostic clinical features of Kawasaki disease is shown in Table 1. Mouth, and oral cavity signs were the most frequent followed by conjunctivitis, and lymph nodes involvement. Rash, hands and feet involvements were the least (Table 2). Table 1 demonstrates other associated clinical features that were found in Kawasaki disease patients. Gastrointestinal symptoms in the form of vomiting, diarrhea, or abdominal pain were the most frequent. In one patient a reaction to IVIG was noticed in the form of hypotension after repeatedly starting IVIG infusion. In 4 patients, hepato-splenomegaly was noticed during the acute phase, but resolved later during follow up.

Diagnosis of patients was made  $8.1 \pm 3.3$  days after start of fever with a range from 4-15 days. All patients received IVIG immediately once diagnosis was carried out even before echocardiography. The IVIG is given in a dose of 2 gm/kg once. Acetylsalicylic acid is given in a dose of 75-100 mg/kg/day in 3 divided doses till the third day after fever subsided, then the dose is adjusted to 5 mg/kg once for 6 weeks. Only patients with coronary affection continued to use acetylsalicylic acid until the last visit. Fever subsided  $1.25 \pm 0.5$  days after IVIG

**Table 1 -** Rate of occurrence of main clinical criteria among patients with Kawasaki disease.

Criteria	n(%)	Onset from fever (mean $\pm$ SD days)
Fever more than 5 days	24(100)	NA
Conjunctivitis	17(70.8)	3.2 $\pm$ 1.7
Mouth and oral cavity	20(83.3)	4.2 $\pm$ 2.9
Hands and feet	12(50.0)	5.7 $\pm$ 3.4
Lymph nodes	18(75.0)	4.4 $\pm$ 3.3
Rash	16(66.7)	4.9 $\pm$ 3.9
NA - not applicable		

**Table 2 -** Other clinical features occurring in patients with Kawasaki disease.

Clinical feature	n(%)
Runny nose	5(20.8)
Irritability	14(58.3)
Diarrhea, vomiting, or abdominal pain	19(79.2)
Decreased food/fluid intake	9(37.5)
Weakness	5(20.8)
Joint pain/arthritis	6(25.0)
Hepatosplenomegaly	4(16.7)
Reaction to immunoglobulin	1 (4.2)

**Table 3** - Laboratory findings in Kawasaki disease patients.

Parameter	Value (mean $\pm$ SD)	Range
Highest leukocytic count (/mm <sup>3</sup> )	14300 $\pm$ 8093.1	4000-42000
Lowest Hb level (gm/dl)	10.2 $\pm$ 1.4	8-13
Highest platelets (/mm <sup>3</sup> )	533.8 $\pm$ 288.9	100-108
Admission ESR (mm/hr)	92.8 $\pm$ 33.4	30-175
Highest ESR (mm/hr)	95.1 $\pm$ 32.3	30-175
Albumin (mg/dl)	26.2 $\pm$ 5	19-35
ALT (IU/L)	51.8 $\pm$ 52.5	17-260
AST (IU/L)	50.3 $\pm$ 52.4	17-254

mm<sup>3</sup> - cubic millimeter, gm/dl - grams (gm) per deciliter, IU/L - units per liter, mg/dl - milligrams per deciliter, mm/hr - millimeters per hour, Hb - hemoglobin, ESR - erythrocyte sedimentation rate, ALT - alanine aminotransferase, AST - aspartate aminotransferase

treatment with a range from 1-3 days. Only 2 patients required another dose of IVIG as fever remained high 48 hours after the initial dose. Echocardiography was performed in all patients 10.1 $\pm$ 3.9 days from onset of fever with a range of 4-20 days. All patients were admitted and the duration of hospital stay was 7.9 $\pm$ 5.8 days with a range from 3-25 days. Patients continued follow up after discharge with echocardiography carried out regularly. The period of follow up from discharge until the last visit was 11.9 $\pm$ 7.4 months with a range from 1.5-31.9 months. Table 3 demonstrates some laboratory parameters that had been performed during admission. The erythrocyte sedimentation rate was high in all patients during admission with a mean of 92.8 $\pm$ 33.4 mm/hr. Applying Japanese Ministry of Health criteria,<sup>10</sup> 3 patients had coronary artery abnormalities. Their age was 0.5, 5, and 6 years. They included 2 boys and one girl. The 6-year-old boy was the patient that developed hypotension each time we attempted to administer IVIG. He was admitted on the eleventh day of illness and fever subsided within 2 days of admission. Echocardiography study at the time of admission revealed coronary artery dilatation of both left main coronary artery (7 mm), right circumflex artery (6 mm), and left anterior descending branch (6 mm). The two other patients were admitted on the ninth day of illness, but echocardiography and diagnosis was not carried out until the eleventh and fourteenth days. Both patients had main left coronary artery dilatation with 5 mm and 6 mm at the time of initial echocardiogram. The coronary artery dilatation continued in all the 3 patients until the last follow up visit.

**Discussion.** The Maternity and Children Hospital is the biggest hospital in Madinah region in Saudi Arabia and serves as a referral center for all pediatric cases with difficult diagnosis. In our hospital, the staff proved to have a high index of suspicion on Kawasaki disease.

During the study period, 51 patients were suspected to have Kawasaki disease, but only 24 patients (47%) were proven to have Kawasaki disease. We recommend to suspect Kawasaki disease even with insufficient criteria for early diagnosis. Late diagnosis of Kawasaki disease carries the risk of delayed immunoglobulin therapy with the possibility of increased chance of coronary arteries affection.<sup>11-13</sup> Most of our patients were below 5 years of age and Kawasaki disease is more common in males than females around worldwide.<sup>14-16</sup> Recurrence and familial occurrence in Kawasaki disease patients is known to happen in some patients,<sup>17,18</sup> but none of our patients had recurrence or family history. Fever is an essential criteria for diagnosis of Kawasaki disease. The original criteria for diagnosis of Kawasaki disease includes fever of  $\geq$ 5 days but recently fever of 4 days was accepted for diagnosis.<sup>19</sup> We have 2 patients diagnosed on the fourth day of illness to have Kawasaki disease. The difficulty in the diagnosis of Kawasaki disease originated in that there is no pathognomonic sign, or specific diagnostic laboratory test. We noticed that distribution of clinical criteria in our patients is in agreement with most previous literature.<sup>9,16,20,21</sup> The protocol in our hospital is to start IVIG for all patients with Kawasaki disease. All patients received IVIG immediately after diagnosis. The mean time for initiation of IVIG was 8.1 days. The key point for prevention of coronary complications is to start IVIG early, before 10 days and preferably within 7 days from onset of fever.<sup>2,6-8,19,22</sup> Delayed treatment carries a high risk and may be of no benefit regarding coronary arteries involvement. We have 3 patients with coronary artery involvements. All patients were referred late to our hospital, at almost around 10 days of illness with prolonged fever with a diagnosis of scarlet fever in 2 patients and as hepatitis in the third patient. As a result, IVIG was started after 10 days of illness. Some patients with kawasaki disease may be misdiagnosed as another illness due to lack of experience of the treating physician. Also, some of these patients may have coronary artery affection as a result of no immunoglobulin therapy. Delayed diagnosis may be attributed to lack of awareness of Kawasaki disease among health workers in peripheral hospitals and primary health care centers. They may misdiagnose this serious disease with a simple one leading to coronary affection with its sequelae of cardiac ischemia, infarction, and death at a young age. This work proves that Kawasaki disease should be considered in the differential diagnosis of children with prolonged fever. A high index of suspicion is needed to detect those patients. Increasing awareness of this disease in health workers in peripheral health centers may help in early diagnosis. A national program of awareness of this serious disease is recommended. This work is limited by being a retrospective study. A prospective multi-center

study will be of great help to assess this disease in all regions in the kingdom of Saudi Arabia.

In conclusion, Kawasaki disease is a serious pediatric disease, and a high index of suspicion is mandatory for early diagnosis. Delayed diagnosis may lead to coronary lesions. Although Physicians in tertiary hospitals have a high level of suspicion, those in peripheral health care units need more awareness. A national awareness program on Kawasaki disease is recommended.

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