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# Overview of Kawasaki Disease in Albaha Area, Saudi Arabia

Abdulmajid Mustafa Almawazini, MD, Ph.D.<sup>1</sup>, Sinan Alnashi, CABP, SSCP.<sup>2</sup>, Ali A. Alsharkawy, CABP, SSCP.<sup>3</sup>,  
Mohammad Abdulmajid Almawazini<sup>4</sup>, Hazem Abdulmajid Almawazini<sup>5</sup>, Mohammed Saad Alzahrani<sup>6</sup>, Saad Ali M.  
Alqahtani<sup>7</sup>

<sup>1</sup> Consultant Pediatric Cardiologist. KFH, Albaha, SA. Email: amawazini@gmail.com. Mobile: 00966508294471

<sup>2</sup> Consultant Pediatrician, KFH, Albaha, SA

<sup>3</sup> Consultant Pediatrician, KFH, Albaha, SA

<sup>4</sup> Pharmacist, KFH, Albaha, SA

<sup>5</sup> Medical Student, Cairo University, Egypt

<sup>6</sup> Pediatric resident, KFH, Albaha, SA

<sup>7</sup> Pediatric resident, KFH, Albaha, SA

Corresponding author: Abdulmajid Mustafa Almawazini, Department of Pediatrics and Neonatology, King Fahad Hospital, Albaha, Zip code 65732-4719. Albaha, Kingdom of Saudi Arabia.

## Abstract

**Background:** Kawasaki disease (KD), an acute, febrile, self-limiting vasculitis of unknown etiology, is a disease that predominantly affects medium- and small-sized arteries of infants and preschool children. **Objectives:** This study aimed to evaluate the presentation and clinical course, diagnosis, management, outcomes, and complications of KD, as well as the presence of abnormal laboratory values therein, among children admitted to King Fahad Hospital, Albaha, Saudi Arabia. **Methods:** This observational, hospital-based retrospective cohort study was conducted at the Department of Pediatrics and Neonatology, King Fahad Hospital Albaha, from 2008 to 2018. Those with both complete and incomplete KD were considered. The diagnostic criteria for KD were based on the European and American Heart Association recommendations. **Results:** The prevalence of KD in Albaha area was 0.6%. It was more common among in male patients (60%) than in female patients (40%). 85% of patients satisfied the diagnostic criteria for complete KD. Among the cases included, 60% were diagnosed during winter and spring. Cardiac abnormalities confirmed through echocardiography were documented in 22.5% of the patients. Abnormal laboratory results were significantly common among those with incomplete KD. **Conclusion:** Majority of patients fulfilled diagnostic criteria of complete KD, and the presence of coronary artery abnormalities consisted with other international published studies. All patients successfully completely recovered during follow-up, and no mortality was documented.

**Keywords:** Kawasaki Disease, Infants, Young Children

**Abbreviations:** KD; Kawasaki Disease. Pts; patients. N; number. CI; Confidence Interval. ESR, erythrocyte sedimentation rate. WBC, white blood cell count. PLTS, platelets. ALT, Alanine Amonitransferase. M; male. F; female. AST; Aspartate Amonitransferase. CI; Confidence Interval. BSA; body surface area. LMCA; left main coronary artery. LAD; left anterior descending. RCA; right coronary artery. CI; confidence interval.

## Introduction

Kawasaki disease (KD) has been described as vasculitis of unknown etiology commonly affecting the medium- and small-sized arteries of infants and children of preschool age [1]. Moreover, first reports of KD were shown in Japan with incidence rates, 264/100,000 individuals, United States and European countries having an

incidence rate of 20.8/100,000 and 8/100,000 individuals, respectively [1-2]. Genetic contributions, familial associations, environmental factors, and infectious diseases, such as novel RNA virus and corona viruses, bacteria, fungi, and house mites, have been associated with KD [1-2-3]. Given that no definitive diagnostic test can confirm KD, diagnostic guidelines established by American Heart Association (AHA) have been used. Accordingly, complete KD is characterized by the presence of fever lasting  $\geq 5$  days with at least four of the following five principal clinical features: (1) bilateral conjunctival injection, (2) cervical lymphadenopathy, (3) polymorphous skin rash, (4) lip or oral mucosa changes, and (5) distal extremity changes [1]. The presence of coronary artery abnormalities may also confirm the diagnosis. Moreover, many complications, such as, neurological, hematological, renal, and gastrointestinal symptoms, have been associated with the disease [1-4-5]. On the other hand, incomplete KD is characterized by fever with  $< 4$  of the principal clinical features, as well as positive laboratory results or coronary artery abnormalities detected through echocardiography [1-6]. Abnormal laboratory parameters in patients with KD include leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP) level, elevated transaminase level, and hypoalbuminemia [1-2-7]. KD has also been considered to be a significant cause of acquired heart disease among children. N-terminal pro-brain natriuretic peptide helps diagnose KD in patients with undifferentiated febrile illness given that it can confirm hematological complications, such as hemophagocytic syndrome and macrophage activation syndrome [2-8]. Early intravenous immunoglobulin (IVIG) and aspirin have been considered the treatment of choice for both complete and incomplete KD [1-2-9]. However, early treatment with corticosteroids, which has been shown to reduce the risk of serious heart problems in children aged  $< 5$  years, can be used for high-risk cases [10-11]. Furthermore, the successful use of infliximab, a monoclonal antibody that binds with high affinity to TNF- $\alpha$  and has been approved for pediatric patients, has been shown in highly resistant KD cases [12-13].

## Objectives

Considering that no study regarding KD has ever been conducted in Albaha, Saudi Arabia, the present study sought to evaluate the clinical course, diagnosis, management, and complications of KD in children with KD admitted to King Fahad Hospital, Albaha. Moreover, laboratory tests, as well as complete and incomplete diagnoses of KD, were also assessed in these children.

## Methods

This observational, hospital-based retrospective cohort study was conducted at the Department of Pediatrics and Neonatology, King Fahad Hospital, Albaha, Saudi Arabia. The study was approved by the research and ethics committee of the hospital. From January 2008 to December 2018, 40 children diagnosed with KD and admitted to our hospital were included in this study, and their medical records were retrospectively reviewed. Diagnostic guidelines established by American Heart Association (AHA) have been used. Accordingly, complete KD is characterized by the presence of fever lasting  $\geq 5$  days with at least four of the following five principal clinical features: (1) bilateral and non purulent conjunctivitis, (2) cervical lymphadenopathy  $> 1.5$  cm, (3) polymorphous skin rash, (4) lip or oral mucosa changes, and (5) distal extremity changes [1]. In some patients, the diagnosis was confirmed despite only 3 or 4 days of fever, provided that classic clinical presentations were observed. Incomplete KD was considered in any infant or child having prolonged unexplained fever and  $< 4$  of the aforementioned clinical features with associated abnormal laboratory results or coronary artery abnormalities detected through echocardiography [1-2-3]. Arthritis or arthralgia, gastrointestinal symptoms, respiratory symptoms, central nervous system findings, and coronary artery abnormalities were recorded as associated clinical findings for all patients. The following laboratory parameters were recorded for the diagnoses of KD: white blood cell count (WBC)  $> 15,000/\text{mm}^3$ , ESR  $> 40$  mm/h, serum CRP  $> 3$  g/dL, platelet count  $\geq 450,000$  after 7 days of fever, albumin levels  $< 25$  g/dL, urine WBC count  $\geq 10$  WBC/hpf, and high Alanine and Aspartate transaminase levels [1-2-3]. Echocardiography was performed when KD was suspected, during which the coronary arteries were imaged and quantitative assessment of luminal dimensions was done. Coronary artery abnormalities were staged according to the following AHA recommendations [2]: grade I, no coronary changes at any stage of the illness; grade II, transient ectasia resolving within the first 6–8 weeks; grade III, small–medium coronary artery aneurysm; grade IV,  $\geq 1$  large or giant coronary artery aneurysms or multiple aneurysms in the same coronary artery; and grade V, coronary artery obstruction. A Z score of  $< 2$  indicated no involvement, 2–2.5 indicated dilation only,  $\geq 2.5$  to  $< 5$  indicated small aneurysms,  $\geq 5$  to  $< 10$  (or absolute dimension  $< 8$  mm)

indicated medium aneurysms, and  $\geq 10$  (or absolute dimension  $> 8$  mm) indicated large or giant aneurysms. Z scores were adjusted for body surface and were considered abnormal when values were  $> 2.5$  [1-2]. Echocardiography was repeated 2 weeks into the treatment and 4–6 weeks thereafter and more frequently in patients determined to have coronary artery abnormalities during the acute illness. Based on our protocol, high-dose IVIG (2 g/kg) was administered as a single intravenous infusion over 10–12 h within 10 days of illness onset and as soon as possible after diagnosis, as well as after the 10th day of illness provided that the fever persisted without any other explanation or with coronary artery abnormalities and laboratory parameters abnormalities. Aspirin (80–100 mg/kg/day) was administered with IVIG till the patient remained a febrile for 48–72h, after which the dose was decreased to 3–5 mg/kg/day as prophylactic treatment for 4–6 weeks [1-2-9]. None of the patients received prednisolone or other medications. P value, Confidence Interval, and statistical analysis was conducted using SPSS version 17.

## Results

As presented in Tables 1 and 2, nearly 85% of the patients were aged  $< 5$  years, while 15% were aged  $> 5$  years ( $P = 0.06$ ). Moreover, 24 patients (60%) were male and 16 (40%) were female ( $P = 0.18$ ). All children had fever lasting for  $> 5$  days. With regard to the five cardinal clinical signs, oral mucosa or lip changes was predominant (95%), followed by cervical lymphadenopathy (92.5%), polymorphous skin rash (90%), conjunctivitis (90%), and distal extremity changes (85%). Gastrointestinal symptoms, one of the associated clinical findings, were observed in 70% of the patients. Cardiac abnormalities (Table 3) were confirmed in nine patients (22.5%), while normal coronaries were observed in 31 (77.5%) ( $P = 0.07$ ). Moreover, all patients suffering from coronary abnormal had coronary artery dilation categorized as stage II with Z scores between 5 and 10. The highest percentage of cardiac impairment was observed within the first 2 years (55%), with no significant differences between males and females ( $P = 0.45$ ). Other common associated clinical findings included arthralgia (45%), hepatic dysfunction, and respiratory symptoms (37%). The abnormal laboratory findings were as follows: elevated WBC (75%), elevated ESR (95%), elevated platelet count (70%), and elevated CRP (60%). Anemia was observed in 45% of the patients, while 25% had low albumin (Table 2). Moreover, 34 patients (85%) satisfied the criteria for complete KD, with the remaining 6 (15%) having incomplete KD ( $P = 0.06$ ). Among the included patients, 13 (32.5%) were diagnosed during summer, 11 (27.5%) during spring, 10 (25%) during autumn, and 13 (32.5%) during winter, 95% CI (7.11–12.8). All patients were administered IVIG immediately after confirming the diagnosis, with responses to treatment being excellent. All patients suffering from cardiac abnormalities successfully completely recovered during follow-up.

**Table 1.** Distribution of patients diagnosed as Kawasaki disease in this study.

Age, month	PTs n = 40		Male = 24 (60%)	Female=16 40%	Complete KD n = 34 (85%)	Incomplete KD n = 6 (15%)	Normal heart n = 31 (77.5%)	Abnormal coronaries n = 9 (22.5%)
5–12	12	(30%)	7	5	10	2	7 (M 4, F 3)	5 (M 3, F 2)
13–24	10	(25%)	6	4	7	3	8 (M 5, F 3)	2 (M, F 1)
25–36	4	(10%)	3	1	4	0	4 (M 3, F 1)	0
37–48	5	(12.5%)	3	2	4	1	5 (M 3, F 2)	0
49–60	2	(5%)	1	1	2	0	1 (M)	1 (F)
61–72	2	(5%)	1	1	2	0	2 (M 1, F 1)	0
73–84	2	(5%)	1	1	2	0	2 (M 1, F 1)	0
85–96	3	(7.5%)	2	1	3	0	2 (M 1, F 1)	1 (M)
95% CI	(2.3-7.7)		(1.3-4.6)	(0.9-3.1)	(2.3-6.2)	(-0.06- 1.8)	(2.1–5.6)	(-0.07-2.3)
82.5% of cases were diagnosed at age $\leq 5$ years and 17.5% at age $\geq 5$ years.								
Winter 13 (32.5%), Spring 11 (27.5%), Autumn 10 (25%), Summer 6 (15%). 95% CI (7.11-12.8)								
PTs: patients. KD; Kawasaki Disease. N; number. CI; Confidence Interval. M; male. F; female.								

**Table 2.** Distribution of Clinical and Laboratory findings in Kawasaki disease.

Clinical findings			Laboratory findings		
Oral findings	95%	38	Elevated ESR $\geq 40$	38	95%
Cervical lymphadenopathy	92.5%	37	Elevated WBC $\geq 15000$	30	75%
Non purulent conjunctivitis	90%	36	Elevated PLTS $\geq 40000$	26	65%
Skin rash	90%	36	Positive CRP	24	60%
Extremity changes	85%	34	Low Albumin $\leq 3$ g/dL	10	25%
Gastrointestinal	70%	28	Elevated ALT $\geq 45$	15	37.5%
Respiratory	25%	10	Elevated AST $\geq 45$	12	30%
Cardiovascular	22.5%	9	Urine $\geq 10$ WBC/f	10	25%
95% CI	(20.1–36.9)		95% CI	(13.4–27.9)	

Abbreviations: ESR, erythrocyte sedimentation rate; WBC, white blood cell count; PLTS, platelets; ALT, Alanine Amonitransferase; AST, Aspartate Amonitransferase. CI; Confidence Interval.

**Table 3.** Patient diagnosed Kawasaki Disease with coronary artery abnormalities, normal ranges and Z scores.

Age/ BSA	LMCA mm	Z score	LAD mm	Z score	RCA mm	Z score
6 months 0.34 cm <sup>2</sup>	4 (1.87–2.46)	5.8	3.4 (1.46–1.81)	8	3.2 (1.43–1.91)	6
7 months 0.37 cm <sup>2</sup>	3.9 (1.93–2.52)	5.4	3.6 (1.50–1.87)	9	3.3 (1.48–1.97)	6.2
8 months 0.41 cm <sup>2</sup>	4 (2.01–2.61)	5.2	3.5 (1.57–1.95)	8.2	3.2 (1.55–2.05)	5
9 months 0.42 cm <sup>2</sup>	4.4 (2.04–2.65)	5.2	3.7 (1.60–1.98)	9	3.4 (1.58–2.09)	5.7
12 months 0.46 cm <sup>2</sup>	4.5 (2.21–2.73)	6.2	4 (1.66–2.05)	9.5	4 (1.64–2.16)	7.2
18 months 0.50 cm <sup>2</sup>	4.2 (2.21–2.84)	5.4	3.9 (1.74–2.15)	8.8	3.9 (1.72–2.26)	6.6
18 months 0.50 cm <sup>2</sup>	4.2 (2.18–2.81)	5.4	3.7 (1.72–2.13)	8	3.4 (1.64–2.16)	5.3
24 months 0.53 cm <sup>2</sup>	4.4 (2.24–2.88)	5.6	3.9 (1.77–2.19)	8.4	3.6 (1.75–2.29)	5.7
60 months 0.74 cm <sup>2</sup>	5 (2.56–3.25)	5.8	4.5 (2.05–2.53)	8.2	3 (2.04–2.64)	2.6
95% CI	4 - 4.57		3.58 - 4		3.22 - 3.66	

BSA; body surface area. LMCA; left main coronary artery. LAD; left anterior descending. RCA; right coronary artery. CI; confidence interval.

## Discussion

Although epidemiological data regarding KD suggest an increase in its incidence worldwide, no study has been published on the incidence or prevalence of KD in Albaha area, Saudi Arabia. Accordingly, the present study showed the prevalence was 0.6%, and 60% of them was  $< 5$  yr. Among the 40 children included herein, 6 (15%) had incomplete KD, which is consistent with the results of other studies [1-2-3-6]. Using published AHA guidelines, including supplementary laboratory criteria, together with echocardiography may lead to better recognition of KD [1]. Accordingly 85% patients satisfied the criteria for complete KD, with the remaining 15% having incomplete KD ( $P = 0.06$ ). 22.5% of patients showed coronary artery abnormalities, and was diagnosed insignificantly more frequent in male patients ( $P = 0.47$ ), albeit not significantly, as documented in published findings [16]. Among the included patients, 13 (32.5%) were diagnosed during summer, 11 (27.5%) during spring, 10 (25%) during autumn, and 13 (32.5%) during winter, [95% CI (7.11–12.8)]. Consistent with other previous data, we found that complete and incomplete KD was more common among children below 1 year [6-14], and insignificantly was higher in male pts ( $p = 0.49$ ) [1-6-15]. In the present study, changes in the oral mucosa or lips (95%) were predominant, followed by polymorphous skin rashes (90%), which is consistent with

other studies [16-17]. Several previous studies have also reported significantly less conjunctivitis, changes in extremities, and cervical lymphadenopathy among patients with incomplete KD [6-14]. However, the present study observed higher rates of the aforementioned changes among those with incomplete KD. Gastrointestinal symptoms (7%), such as abdominal pain, vomiting, and diarrhea, and arthralgia (50%) were common non classical signs observed herein, a finding consistent with those in worldwide studies [4-14]. Moreover, among the nine (22.5%) patients with cardiovascular complications observed herein, five had complete KD and four had incomplete KD, which was not consistent with other published studies wherein incomplete KD was found to be associated with higher risk of developing coronary abnormalities [2-6]. All children with cardiovascular complications who received IVIG experienced complete recovery of coronary artery abnormalities. Furthermore, abnormal laboratory results observed herein coincided with those published previously [1-14-17] and were able to accurately reflect the severity of the disease.

**One limitation** of the present study is the considerably small sample size. As such, the findings should be considered no conclusive.

## Conclusions

In conclusion, KD was more common in children less than 5 years, complete KD was diagnosed more frequently than incomplete, and in male patients more than in female patients. Moreover, most of the cases were diagnosed during winter and spring. Cervical lymphadenopathy and changes in distal extremities, as well as abnormal laboratory results, were significantly more common among those with complete KD than those with incomplete KD. All patients responded remarkably to treatment with IVIG and aspirin.

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