Kawasaki syndrome: the Iranian experience

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متلازمة كاوازاكي: الخبرة الإيرانية

إسماعيل صادقي ورضا أمين وحسين عجمي

خلاصة: تعرض هذه المقالة الخبرة المكتسبة من خمسين حالة من متلازمة كاوازاكي في جمهورية إيران الإسلامية. إن هذه المتلازمة تحدث غالباً في الشتاء والربيع، وتبلغ نسبة الذكور المصابين بها إلى الإناث 2.1 : 1. لقد حدث المرض في 72% من الحالات فيما بين سنة واحدة إلى خمس سنوات من العمر. وفي 80% من الحالات كان هناك مرض فيروسي أو جرثومي سابق. ووجدت لدى ثمانية مرضى (16%) بيّنات ميكروبيولوجية على العدوى بينما كانت لدى 19 حالة (38%) بيّنات سريرية. وظهرت لدى خمسة مرضى دلائل سريرية وشعاعية على التهاب الجيوب. وكانت كثرة الكريات البيض، وكثرة العَدلات، وارتفاع سرعة تثفل الكريات الحمر، وإيجابية البروتين التفاعلي "C"، وانعكاس النسبة بين الألبومين والغلوبولين، وارتفاع عيار أضداد الحالّة العقدية "O"، هي من العلامات الأخرى على وجود العدوى والالتهاب. كما أن الذكورة والحمى الطويلة وزيادة عدد الكريات البيض على 15 000 في المليمتر المكعب وزيادة عدد المحبّبات المطلق على 10 000 في المليمتر المكعب كانت علامات اخطار مهمة للإصابة بأمراض الشرايين التاجية (في عشرة مرضى). ومن بين 35 مريضا تلقوا الغلوبولين المناعي بالوريد، أصيب ستة مرضى (17.3%) بأمراض الشرايين التاجية على الرغم من بدئهم المعالجة بالغلوبولين المناعي في الأيام العشرة الأولى للمرض.

ABSTRACT Experience with 50 cases of Kawasaki syndrome in the Islamic Republic of Iran is presented. The syndrome occurred mostly in winter and spring with a 2.1:1 male:female ratio. In 72% of cases, the disease occurred between 1 and 5 years of age, and 80% had an antecedent viral or bacterial illness. Eight patients (16%) had microbiological evidence of infection and 19 (38%) had clinical evidence. Five patients had clinical and radiological evidence of sinusitis. Leukocytosis, neutrophilia, bandaemia, elevated erythrocyte sedimentation rate, positive C-reactive protein, reversed albumin/globulin ratio and increased antistreptolysin O titre were other indications of infection and inflammation. Male gender, prolonged fever, white blood cell count > 15 000/mm^3 and absolute granulocyte count > 10 000/mm^3 were significant risk factors for the development of coronary artery disease (10 patients).

Le syndrome de Kawasaki : l'expérience iranienne

RESUME L'expérience relative à 50 cas de syndrome de Kawasaki en République islamique d'Iran est présentée. Le syndrome survenait principalement en hiver et au printemps avec un ratio homme/femme de 2,1:1. Dans 72 % des cas, la maladie survenait entre l'âge d'un an et de 5 ans, et 80 % avaient eu une maladie virale ou bactérienne auparavant. Chez huit patients (16 %), il y avait des preuves microbiologiques de l'infection et chez 19 (38 %), il y avait des preuves cliniques. Cinq patients avaient des preuves cliniques et radiologiques de sinusite. La leucocytose, la polynucléose neutrophile, la bandémie, une vitesse de sédimentation globulaire accélérée, la protéine C-réactive positive, un rapport albumine globuline inversé et l'augmentation du titre d'antistreptolysine O étaient d'autres indications d'une infection et d'une inflammation. Le sexe masculin, une fièvre prolongée, un chiffre de leucocytes > 15 000/mm^3 et une numération absolue des granulocytes >10 000/mm^3 étaient des facteurs de risque importants pour le développement des coronaropathies (10 patients).

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Introduction

Kawasaki syndrome (KS) was first recognized by Dr Tomisaku Kawasaki in 1961. In 1967, he published a report of his experience with 50 cases of KS in Japanese [*1*] and in 1974 in English [*2*]. Concurrent and further recognition of the disease was made in Hawaii by Melish et al. [*3*]. The disease has been recognized worldwide [*4*] and is now an important cause of acquired heart disease in children.

Methods

The first case of KS in the Islamic Republic of Iran was diagnosed by Sadeghi in Shiraz in February 1980 and the second case 6 months later. For reasons unknown, no further cases were recorded for 10 years. From 1990 until early 1997, however, 48 cases were seen in Shiraz University hospitals. This study is a prospective study of KS in children of southern Islamic Republic of Iran.

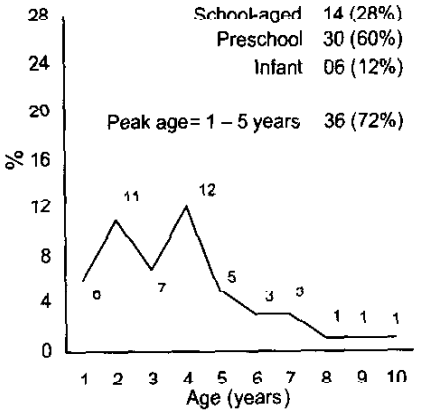

Figure 1 **Age distribution of the 50 patients with Kawasaki syndrome**

Results and discussion

Sex

Of the 50 KS cases, 34 (68%) were male and 16 (32%) were female (ratio = 2.1:1). There were more males in this group of patients compared with the ratio of 1.3–1.4:1 for the general paediatric population in this area [*5*]. Our male:female ratio was greater than the male:female ratio in Japanese children (1.5:1) [*2*] and American children (1.6:1) [*6*] with KS.

Age

Figure 1 shows the age distribution of the children with the disease. The youngest patient was a 13-month-old male and the oldest a 13-year-old male. Although the disease peaked twice, between ages 2–3 years and 4–5 years, incidence declined after age 5 years until the early teen years, beyond which the disease is uncommon.

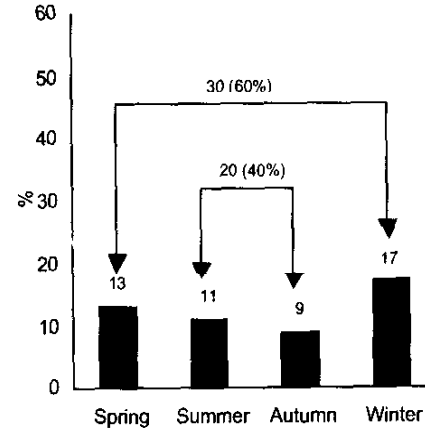

Figure 2 **Seasonal distribution of Kawasaki syndrome in the 50 patients**

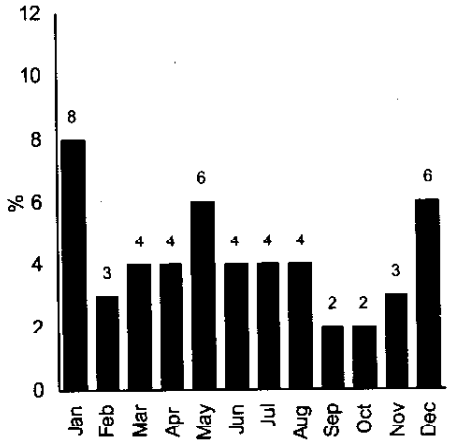

Figure 3 **Monthly distribution of Kawasaki syndrome in the 50 patients**

The mean age was 4.5 years, higher than Japanese and American mean ages of 1.5 years and 2.7–4.2 years respectively [*6,7*].

Season

Figures 2 and 3 show the seasonal and monthly distribution of the patients presenting with the disease respectively. More patients were seen during winter and spring than summer and autumn. The disease peaked in December, January and May and had the lowest incidence during September and October. In Japan, the disease is common all year, with the ratio of cases seen in the peak summer months to those seen in the lowest winter months about 10:7 (1.4:1). In our study, the ratio of cases seen in the peak winter months to those seen in the lowest autumn months was 17:9 (1.8:1). Our finding is similar to the report of Bell et al. [*6*] showing peak seasonal incidence of KS in winter and spring.

Antecedent illness and medical history

Of the 50 patients, 37 (74%) had experienced an upper respiratory tract illness within 30 days of the diagnosis of KS. These illnesses consisted of 20 (40%) cases of pharyngitis, 6 (12%) cases of scarlet fever, 5 (10%) cases of cervical adenitis, 3 (6%) cases of common cold/rhinitis, 2 (4%) cases of mumps and 1 (2%) case of otitis media. Pre-existing medical conditions were limited to asthma in 1 patient. The other 12 children were apparently healthy prior to diagnosis of KS.

All the patients had been seen by an outside physician and all had received antibiotics, including penicillin, ampicillin, amoxicillin, cephalothin, erythromycin, gentamicin and trimethoprim/sulfamethoxazole; 26 (52%) patients had received two or more antibiotics prior to their admission to hospital. The sister of one patient had been diagnosed with KS 3 years before the development of the disease in her brother. There was a history of rug shampooing in 3 patients.

Table 1 **Patients fulfilling the diagnostic criteria of Kawasaki syndrome**

Criteria	No. of patients (n = 50)	%
Fever	50	100
Changes in the oropharyngeal mucosa	49	98
Bilateral nonpurulent conjunctivitis	46	92
Changes in the extremities	42	84
Rash	42	84
Cervical lymphadenopathy	41	82

Clinical manifestations

The major signs and symptoms of the patients are presented in Table 1. All 50 cases had fever; 40 patients (80%) had a temperatures of 40 °C or higher, 9 (18%) had a temperature of 38–39 °C and only 1 patient had a temperature of less than 38 °C upon admission. The mean duration of fever was 14.2 days (range 6–39 days), which is similar to the Morens et al. study [7] which reported a mean fever duration of 11.8 days with a range of 5–39 days. The temperature pattern was spiky in the majority of our patients. In our study, 24 (48%) patients had fever, as well as all the five other diagnostic criteria set by Kawasaki [1,2], and 26 (52%) had fever plus four out of five of the diagnostic criteria.

Changes in the oropharyngeal mucosa included erythema, fissuring, cracking or bleeding of the lips in 45 (90%) patients, strawberry tongue in 35 (70%) and diffuse erythema of the oropharyngeal mucosa in 42 (84%). Changes in the extremities included erythema and firm indurative oedema of the palms and soles, with oedema of the hands and feet in 40 (80%) patients. Also, 37 patients (74%) developed desquamation, which involved the periungual area in 17 patients, distal extremities in 10 patients, palms and soles in 6, generalized in 2, facial in 1 and perineal in 1 patient. The rash was generalized as maculopapular and morbiliform in 36 patients, scarlatiniform in 4, erythema multiform-like in 1, and urticarial in another. Cervical lymphadenopathy

Table 2 **Symptoms and signs of Kawasaki syndrome found in the 50 patients**

Symptom	No.	%	Sign	No.	%
Vomiting	28	56	Tachycardia	50	100
Sore throat	20	40	Heart murmur	16	32
Cough	20	40	Hepatomegaly	16	32
Arthralgia and/or arthritis	20	40	Chills	7	14
Abdominal pain	18	36	Generalized oedema	7	14
Diarrhoea	17	34	Splenomegaly	4	8
Headache	10	20	Abdominal distension	4	8
Rhinorrhoea	9	18	Stomatitis	4	8
Constipation	7	14	Purulent rhinitis	2	4
Irritability	5	10	Purulent conjunctivitis	2	4
Jaundice	4	8	Lymphadenopathy: other parts	2	4
Tea-coloured urine	4	8	Sweating	2	4
Dysuria	3	6	Pallor	2	4
Drowsiness	3	6	Cyanosis	2	4
Epistaxis	3	6	Melena	1	2
Back pain	2	4	Thrush	1	2

was unilateral in 29 patients (on the right in 12 and on the left in 17) and bilateral in 13 patients.

Associated signs and symptoms of KS, as shown in Table 2, involved multisystem organ involvement of the upper respiratory tract, gastrointestinal system, and musculoskeletal system. They were mostly non-specific and self-limiting.

Arthritis and/or athralgia

Arthritis and/or arthralgia developed in 20 (40%) patients, 1 with monoarticular and 19 with the polyarticular type. Polyarticular joint disease involved both large and small, and upper and lower extremities. Regarding onset, 18 patients (90%) had the onset of arthritis in the acute stage of the disease and 2 (10%) in the subacute and convalescence stage. One patient initially presented with bilateral knee effusion and joint fluid with a white blood cell count (WBC) of > 90 000/mm^3 and polymorphonuclear leukocyte predominancy. He responded to antibiotics but developed signs and symptoms of KS. Early-onset arthritis in the other patients had a self-limiting course. Of the 2 patients with late-onset arthritis, 1 developed polyarticular arthritis for 2½ years and eventually responded to chloroquine treatment.

Hicks and Melish [*8*] described two types of arthritis in the course of KS. Early-onset type, which occurred in the first week of illness, constituted one-third of cases and tended to involve multiple joints. including the small interphalangeal joints as well as the large weight-bearing joints, intense inflammatory reaction and poor response to all nonsteroidal anti-inflammatory drugs (NSAIDS). Late-onset arthritis (developing after the 10th day of the illness), involved two-thirds of the patients, and had a predilection for the large weight-bearing joints, especially the knees and ankles. It was associated with less intense inflammation and was immune-complex mediated [*9*]. No chronic arthritis was observed.

Gall bladder disease

In our patients, 10 (20%) developed hydrops of the gall bladder during the first 2 weeks of illness. The gall bladder either had a thick wall and/or distension seen by ultrasonography. One patient had a huge and markedly distended gall bladder with sludge in the lumen. In another patient, the distension also included the common bile duct. In 3 patients, gall bladder distension was associated with ascites.

The most common symptoms were abdominal pain, accompanied by vomiting and abdominal distension. Of the 10 patients, 6 had associated hyperbilirubinaemia, bilirubinuria and elevated serum aminotransferases. All 10 patients made a full and uneventful recovery.

Gall bladder hydrops is a benign and self-limiting complication of KS, as noted by others [*10,11*]. Surgical intervention should be reserved for non-resolving gall bladder obstruction and organ necrosis, as operative intervention may increase the rate of complications [*11*].

Laboratory findings

The laboratory findings are listed in Table 3. The majority of our patients presented with leukocytosis (WBC > 10 000/mm^3) and neutrophilia. Absolute band count of > 500/mm^3 was noted in 14 (28%) patients. Erythrocyte sedimentation rate (ESR) of more than 30 mm/hour, positive C-reactive protein (CRP) and thrombocytosis were seen in 89.1%, 90.9% and 80.0% of our patients respectively. Of the 40 patients with a platelet count > 450 000/mm^3, 16

Table 3 **Laboratory findings in the patients with Kawasaki syndrome**

Variable	No. +ve /No. tested	%
Leukocytosis: white blood cell count (/mm^3)		
> 10 000	44/50	88.0
> 15 000	30/50	60.0
≥ 20 000	19/50	38.0
Absolute neutrophil count (/mm^3)		
≥ 2500	50/50	100.0
≥ 5000	47/50	94.0
≥ 10 000	32/50	64.0
Absolute band count > 500/mm^3	14/50	28.0
ESR > 30 mm/hour	41/46	89.1
C-reactive protein positive	30/33	90.9
Platelet count > 450 000/mm^3	40/50	80.0
Peak thrombocytosis (2nd and 3rd weeks)	37/40	92.5
Reversed albumin/globulin ratio	17/25	68.0
Hyperbilirubinaemia	12/25	48.0
ALT and AST elevation	10/25	40.0
Pyuria	21/50	42.0
Haematuria	9/50	18.0
Bilirubinuria	8/50	16.0
Proteinuria	6/50	12.0
Antistreptolysin O titre > 400 U	5/12	41.7
Anaemia (haemoglobin < 12 g/dL)	40/50	80.0

ESR = erythrocyte sedimentation rate.
ALT = alanine aminotransferase.
AST = aspartate aminotransferase.

(40%) recorded a count of > 900 000/mm^3; the highest recorded platelet count was 1 902 000/mm^3. Thrombocytosis peaked in the second and third weeks of the illness in 92.5% of the patients.

Reversed albumin/globulin ratio, hyperbilirubinaemia and serum aminotransferase elevation was noted in 68%, 48% and 40% of our patients respectively. Urinalysis revealed sterile pyuria in 42% of the patients, haematuria in 18%, bilirubinuria in 16% and proteinuria in 12%. No patient exhibited abnormal kidney function tests. Throat culture was positive for group A β-haemolytic streptococci in 4 patients and non-group A streptococci in 1 patient. Two patients developed purulent conjunctivitis, with coagulase-positive *Staphylococcus aureus* isolated from their eye discharge. Antistreptolysin O (ASO) titre above 400 U was noted in 41.7% of the patients. In 5 patients who had clinical sign of sinusitis, X-ray revealed sinusitis. We found 40 (80%) patients had anaemia (Hb < 12 g/dL); 20 (40%) had Hb < 10 g/dL and 5 (10%) had Hb < 7 g/dL. Two patients required transfusion.

There is no single laboratory test or combination of laboratory tests to diagnose KS [*12*], but levels of acute-phase reactants, as measured by total WBC count, ESR, CRP and serum α-2 globulin are consistently elevated or increased with the onset of fever and persist for 6–10 weeks [*13,14*]. They can help to differentiate KS from diseases with similar presentations, direct for the possible etiology and may have a prognostic value in predicting complications of the disease.

Cardiovascular complications

Cardiovascular complications are the most common and serious cause of both short- and long-term morbidity and mortality in patients with KS, as noted by earlier reports [*2,3*]. In our study, 10 (20%) patients developed cardiac complications, mainly of coronary artery involvement. Table 4 shows the common characteristics of KS

Table 4 **Characteristics of patients with Kawasaki syndrome with cardiac complications compared with those without cardiac complications**

Variable	Cardiac (n = 10)		Non-cardiac (n = 40)		P-value
Sex ratio (M:F)	4:1		1.8:1		0.47
Mean hospital stay (days)	12.7		10.4		
Febrile course (days)	17.8		13.3		
	No. +ve/ No. tested	%	No. +ve/ No. tested	%	
Age (years)					
< 2	2/10	20.0	3/40	7.5	0.6
2–5	8/10	80.0	23/40	57.5	
Platelet count (> 450 000/mm^3)	8/10	80.0	24/30	80.0	
Peak thrombocytosis (2nd and 3rd weeks)	9/10	90.0	28/30	93.3	
Erythrocyte sedimentation rate > 30 mm/hour	8/9	88.9	33/37	89.2	
C-reactive protein positive	9/10	90.0	21/23	91.3	
White blood cell count (/mm^3)					
> 10 000	10/10	100.0	33/40	82.5	0.16
> 15 000	8/10	80.0	21/40	52.5	
Absolute granulocyte count > 10 000/mm^3	9/10	90.0	15/20	75.0	< 0.04
Clinical and microbiological evidence for infection	8/10	80.0	–	–	

patients with cardiac versus non-cardiac disease. Of the 10 patients with cardiac complications, 8 (80%) were male (male:female ratio = 4:1). The ratio for non-cardiac patients was 1.8:1 (P = 0.47). All cardiac patients were between 1 year and 5 years old, whereas 26 of the 40 (72%) non-cardiac patients were in this age group. (P = 0.6). The difference was not statistically significant but our data show that, unlike other studies [*15,16*], the majority of our patients and those with cardiac involvement were preschool children rather than infants.

Other risk factors for coronary artery disease, like platelet count, peak thrombocytosis, maximal ESR, CRP and WBC > 10 000/mm^3 for the children with coronary disease were comparable with children with normal coronary arteries. WBC count of ≥ 15 000/mm^3 and absolute granulocyte count (AGC) of > 10 000/mm^3, on the other hand, were reported in 80% and 90% of cardiac patients versus 52.5% and 75% of non-cardiac patients respectively (P = 0.16 and P < 0.04). The mean hospital stay was not different, but the mean duration of

fever was higher in patients with coronary artery disease: 17.8 days versus 13.3 days ($P = 0.31$). The left coronary artery was involved in 8 patients, the right coronary artery in 4 and both arteries in 4 patients. One patient developed myocarditis and 3 developed valvulitis. Cardiac involvement was evident in 4 patients in the second week, 3 patients in the third week and 3 patients in the fourth week of illness. Only 1 patient manifested aortic dilatation 13 months after KS was diagnosed, and no patient died of coronary artery disease.

Identification of patients at risk for coronary artery involvement was first proposed by Asai [*17*]. Nakano [*15*] reported a more precise scoring method that can be used early in the course of the disease to predict high-risk patients. Unlike our findings, he found that the age at onset, and the CRP and platelet counts contributed significantly to the criteria for scoring such patients. More recently, laboratory tests using specific immunologic and metabolic reactions have been proposed as predictors of vascular inflammation [*18,19*].

Searching for the etiology

The epidemiological characteristics of KS (seasonal preponderance, clinical presentation, and the existence of epidemic outbreaks) suggest an infectious etiology [*12*]. A variety of non-infectious agents [*20*], infectious agents, such as viruses [*21*], fungi and toxin-secreting staphylococci and group A streptococci [*22,23*], have been suggested as possible microbial etiological agents.

Various clinical and laboratory data in our study indicated a microbial etiology for KS. The clinical evidence was: sinusitis in 5 patients, pneumonia in 4 and individual cases of septic arthritis, pharyngeal abscess, adenitis, bacterial meningitis and urinary tract infection. Laboratory evidence included: leukocytosis with neutrophilia and bandaemia, pyuria, elevated ESR, positive CRP, reversed albumin/globulin ratio, positive throat culture for β-haemolytic streptococci, positive eye culture for staphylococci and elevated ASO titre. This is further supportive evidence for a microbial etiology.

Among localized infections, sinusitis was an interesting finding noted in 5 (10%) patients (5 of 10 for whom sinus X-rays were taken). Such a hidden infection and other localized infections may be important foci for organisms, notably toxin-producing staphylococci and streptococci, to act as a superantigen, inducing hyperactive immune response [*23,24*].

Treatment

All the patients received anti-inflammatory doses of aspirin. In addition, 35 (70%) received intravenous immunoglobin (IVIG) (27 patients received a single dose, 8 patients received a 4-day dose). Among the 10 cardiac patients, 8 (80%) received IVIG, 6 during the first 10 days of the illness, 1 on day 12, and the other on day 33. Furthermore, 5 of the 10 (50%) cardiac patients required treatment with dipyridamole. Of all the patients, 10 were afebrile when aspirin was started, 30 (75%) became afebrile on or before the fifth day and 10 became afebrile after the fifth day of treatment. Of the 35 patients who received IVIG, all were afebrile on the fifth day. At the 3-month follow-up, there was no significant difference ($P = 0.7$) between patients who received IVIG and those who did not receive the immunoglobulin with regard to the development of coronary artery disease.

Early treatment of KS with aspirin and high-dose IVIG has proved to be effective in reducing clinical symptoms, as well as reducing the prevalence of coronary aneurysm to approximately 5%. The single-dose regimen for IVIG is now the standard recommended initial mode of therapy [*25*]. The majority of patients experienced defervescence within 48 hours. Retreatment with IVIG has been successful in patients who do not respond fully or have fever recrudescence after initial treatment with intravenous gamma globulin. None of the patients who received initial treatment with IVIG required retreatment.

Conclusion

KS is a common disease in the Islamic Republic of Iran. The disease was more prevalent in males and occurred mostly in winter and spring months. Children between ages 1 year and 5 years were most affected. We found 80% of our patients had an antecedent viral or bacterial illness. All the patients met the diagnostic criteria for the disease. All had fever and 38% of the patients had clinical, 16% microbiological and 10% radiological evidence of infection. Other evidence of infection and inflammation included leukocytosis, neutrophilia, bandaemia, ESR elevation, positive CRP, reversed albumin/globulin ratio and increased ASO titre.

Male gender, prolonged fever, WBC > 15 000/mm^3 and AGC > 10 000/mm^3 were significant risk factors for developing coronary artery disease. Treatment with aspirin and IVIG resolved the symptoms quickly but did not significantly alter the development of coronary artery disease. An infection, especially a hidden one, should always be sought as an etiology of KS.

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