<u>Research Article</u>

Kawasaki Disease - Diagnosis and Management- A Retrospective Study

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Abstract: Kawasaki disease (KD) is an acute febrile illness, mostly of under-fives. It is the leading cause of acquired heart disease in children in the developed countries, with coronary artery abnormalities in 20-25% of untreated patients. This is a retrospective study of patient records of cases of KD in 5 years at Sohar hospital, Oman looking at epidemiology, clinical presentation, investigations and management. In our study, KD occurred mostly in boys under 5,in the first half of the year. All had fever. In decreasing frequency, they had oral mucosal changes, cervical lymphadenopathy, rash, conjunctivitis and extremity changes. Most had raised CRP/ESR, raised platelets, and low haemoglobin. Less than half had a raised white cell count. Serum albumin was done in 44% of admissions, of which 37.5% had low values. 50% admissions had urine microscopy done. Blood cultures, urine cultures, ASOT, Monospot, viral studies, ALT were also done and were all mostly normal. Ultrasound neck was done in one case and chest X-ray in two cases. ECHO showed some abnormality in 50% admissions. 16.7% cases were typical KD, 72.2 % incomplete KD. All (100%) children received the recommended treatment. 5.5% of admissions was unresponsive to IVIG, and responded to methylprednisolone. Our study demonstrates recognition of KD in children in Oman, mostly presenting as incomplete KD. All children(100%) received the recommended treatment.
Keywords: child, coronary artery disease, epidemiology, kawasaki disease, Oman, retrospective studies

INTRODUCTION

Kawasaki disease (KD) is an acute febrile illness of childhood with possible long term cardiac complications. It occurs mostly in children with an Asian background. It has been referred to in the past as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa.

KD is usually an illness of the under-fives, in boys more than girls. It was first described in Japan by Tomisaku Kawasaki in 1967.

KD is the leading cause of acquired heart disease in children in most developed countries, including the USA and Japan. In Japan, >200,000 cases of KD have been reported since the 1960s.. During the 5 year span between 2001- 2006 worldwide incidence increased by >30 %. KD is a vasculitis with a predilection for the coronary arteries, and approximately 20-25% of untreated patients experience coronary artery abnormalities, including aneurysms [1]. The exact cause of the disease is not known, but relationship to infection [2], immunological causes and genetics has been postulated. There is considerable research going on currently worldwide on various causative, diagnostic and treatment aspects of this disease.

The illness has been described in three phases - acute, subacute and convalescent. The acute phase is characterized by fever, and accompanied by a combination of other specific clinical features. Serious complications of KD like coronary artery dilatations and aneurysms are seen in the subacute phase . In the convalescent phase, there may be progression or decline of previous complications.

The diagnostic criteria for typical KD include-Fever persisting at least 5 days with presence of at least 4 principal features:
1. Extremity changes-Acute phase: Erythema of palms, soles; edema of hands, feet
      Subacute phase: Periungual peeling of fingers and toes
2. Polymorphous exanthem
3. Bilateralnon exudative bulbar conjunctival injection

4. Changes in lips and oral cavity: Redness, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae

5. Cervical lymphadenopathy (>1.5-cm diameter), usually unilateral, and exclusion of other diseases with similar findings

6. Characteristic investigation results which aid diagnosis include platelet count > 4,50,000/ cumm from day 7, WCC (White cell count) > 15000/ cumm, CRP (C reactive protein)> 3 mg/dl, ESR (Erythrocyte sedimentation rate)> 40mm/hr, anaemia -normocytic normochromic, albumin < 3 g/dl, Pyuria > 10 / HPF (High power field) , ALT (Alanine amino transferase) > 50 U/ L .The criteria to diagnose atypical Kawasaki disease are -Elevated CRP and/or ESR and three or more abnormal laboratory findings (as above) / abnormal echocardiogram (ECHO) [3].

The clinical presentation of Kawasaki disease may mimic some common conditions in Paediatrics like scarlet fever, viral infections- eg- measles, sometimes Steven Johnson syndrome or toxic shock syndrome. In such cases, appropriate investigations to rule out these conditions may be requested considering each individual presentation.

In a study in Oman in 2003, an elevated ESR(91.7 per cent) and a raised CRP (92.3 per cent) were the most significant laboratory findings [4].

Intravenous immunoglobulin and aspirin given 5-10 days after onset of fever reduce the incidence of coronary artery lesions from around 20% to around 5% [5] . Coronary artery involvement is usually maximal within 6 to 8 weeks after the acute episode [6].

Kawasaki disease may cause coronary artery damage, long-term cardiovascular morbidity and occasionally mortality, especially if the diagnosis is missed or timely treatment is not given.

The treatment regimen includes IVIG (Intravenous immunoglobulin) in the dose of 2 grams/ kg/ day as a single intravenous infusion over 10-12 hours IV methyl prednisolone has been used in refractory cases (30 mg/kg/day IV for one to three days). High-dose aspirin is administered initially for its anti-inflammatory effect [7]. Oral aspirin is advised initially in the dose of 80-100 mg/ kg/ day (high dose) till the acute inflammation subsides, and then low dose 5 mg/ kg/ day is to be continued for 6-8 weeks. In a study, Cyclosporin A (CyA) treatment in patients with refractory KD has been evaluated [8]. Newer treatments being studied include plasmapheresis, antitumour necrosis factor, cyclophosphamide, cyclosporine.

Furthermore, the long-term prognosis of patients who receive intravenous immunoglobulin and other therapies must be determined [9]. The majority of patients with KD appear to have a benign prognosis, but a subset of patients with coronary artery aneurysms are at risk for ischemic events and require lifelong treatment [10].

EXPERIMENTAL SECTION
Objectives
The objectives of this study included –
1. Studying the children diagnosed and treated as Kawasaki disease in Sohar hospital, Oman for a retrospective period of 5 years.
2. Evaluating the diagnostic basis, and management with accepted standards.
3. Documenting the increasing awareness of KD in Sohar, Oman at the present time.

Methods
The study is retrospective, looking at the patient records of all children diagnosed and treated as Kawasaki disease in 5 years at Sohar Hospital, Oman.

Inclusion criteria
The study sample included all children (birth up to age 12) admitted and treated as Kawasaki disease in Sohar hospital during the period of 5 years (1st November 2008 till 1st November 2013).

Exclusion criteria
Children who did not fit into the clinical/ laboratory/ ECHO criteria for diagnosis as typical or atypical Kawasaki disease are excluded.

We looked at the age range, sex, month of presentation for any seasonal variation, duration of hospital stay, area the patient comes from, presenting clinical features, investigations, any abnormality in ECHO, diagnosis- whether typical or incomplete Kawasaki disease, and follow-up, treatment with IV Immunoglobulin, and oral aspirin, whether any 2nd dose of IVIG was given, whether methyl prednisolone was given after IVIG.

We looked at the results of investigations recommended for purpose of diagnosis and prognosis of KD- white cell count, haemoglobin, platelet count, CRP, ESR, Albumin levels, ALT, pyuria. We examined when ECHO was done, if it showed any abnormalities, and repeat ECHO reports in all cases, and follow up.

Data management
Data collected and analysed in SPSS.

Statistical analysis
Statistical analysis included tabulating distribution (age, sex, hospitalisation) as percentages of total cases, occurrence of each clinical feature as

percentage of total cases, charting significant abnormal laboratory investigations, and tabulating the cardiac abnormalities in ECHO in all cases with abnormal ECHO reports.
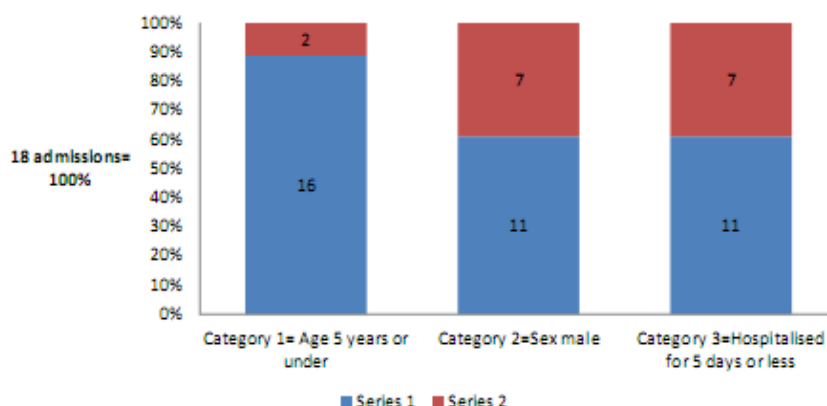
RESULTS
Epidemiological data

Of the 18 admissions, 2 were aged above 5 years, all the others were under 5. The youngest age was 4 months. The oldest was a 7 year old boy. The number of children admitted under 1 year of age was seven. Sex distribution showed 11 out of 18 admissions to be boys.
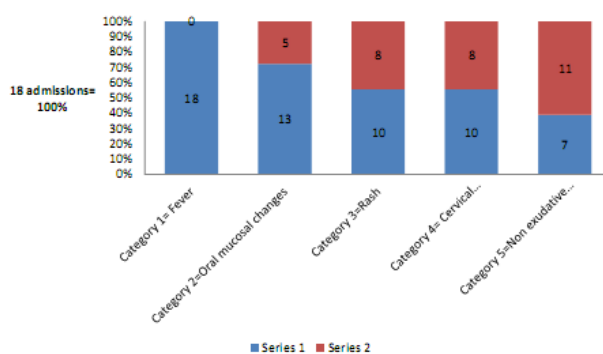
The longest period of hospitalization was 11 days, and the shortest was 1 day, average being- 5.5 days. One child, the 4 month old boy, was readmitted 2 days after being discharged. One child – a 1 year old boy from Suwaiq was admitted 1 year after being treated , with the same diagnosis and treatment.

16 children are from the North Batinah Governate (wilayat Sohar-6, Saham-4, Suwaiq-3, Shinas-2, Khaburah-1) and one child from the Musandam governate (wilayat Khasab). 11 out of the 18 admissions were in the period of the year between January and June. The other 7 admissions were between July and December (figure 1).

Fig-1: Epidemiology data

Fig-2: Clinical presentation

Table 1: Clinical presentation

Clinical characteristics	Present (Out of 18 admissions)	Frequency (% of total admissions)
Fever	18	100
Oral mucosal changes	13	72
Rash	10	55.5
Cervical lymphadenopathy	10	55.5
Non exudative conjunctivitis	7	38.8
Extremity changes	4	22

Clinical presentation

The clinical findings were distributed as follows-

1. Fever- All 18 admissions
2. Oral mucosal changes- 13 out of 18 admissions
3. Cervical lymphadenopathy- 10 out of 18 admissions
4. Rash- 10 out of 18 admissions
5. Non-exudative conjunctivitis was seen in 7 out of 18 admissions
6. Extremity changes were noted in 4 out of 18 admissions

Other symptoms reported- Diarrhoea and vomiting- 1 case. Diarrhoea- 1 case. Vomiting- 5 cases, Cough- 2 cases. All these symptoms ranged from 1 – 5 days duration (figure 2, table 1).
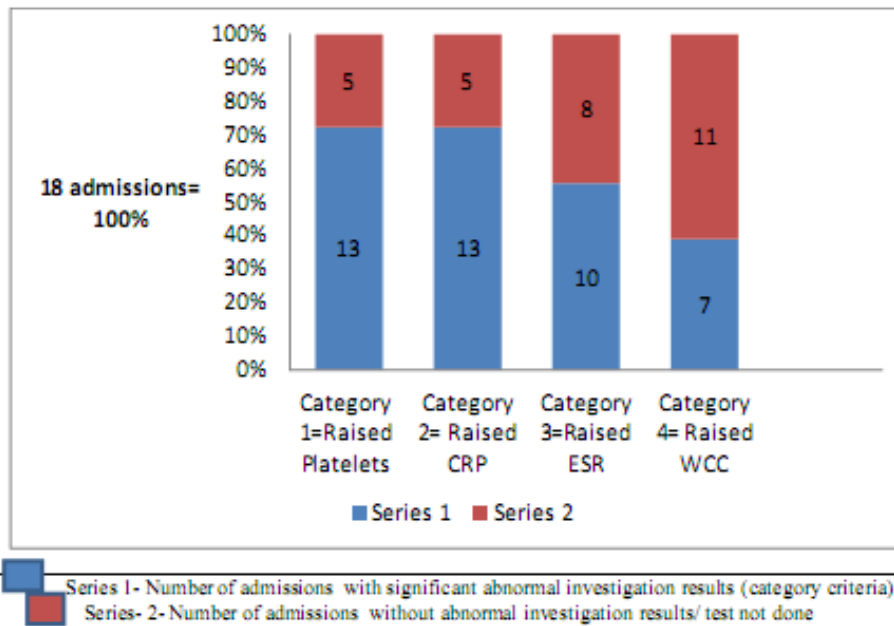

Series 1- Number of admissions with significant abnormal investigation results (category criteria)
Series- 2- Number of admissions without abnormal investigation results/ test not done

Fig-3: Investigations

Investigations

Raised platelets > 4,50,000 - 13 out of 18 admissions

CRP > 3 mg/ dl- Was seen in all the cases- 13 out of 18 admissions in which CRP was done. 4 admissions did not have it done, and in 1 case, it was not reported.

ESR> 40 mm/ hour- 10 admissions. It was not done in 5 admissions, and in 3 admissions was < 40 mm/ hr.

Haemoglobin ,< 10 g/dl or fall on repeat Hb level – 10 out of 18 admissions

WCC > 15,000 - 7 out of 18 admissions

Urine WCC/ cu mm- Done in 9 admissions, of which in 2 cases not reported. 2 cases had 8, and 5 admissions had 4 WCC/ cumm

Albumin < 30 G/L- 3 admissions. It was not done in 10 admissions. In 5 admissions, it was above 30 G/L (and not repeated)

ALT > 50 U/L- 1 admission. Not done in 11 admissions. The value was < 50 U/L in 6 admissions.

Other investigations done include-

Blood C&S-Done in 13 cases- 12 cases- Negative. 1 case- contaminant

Urine C & S- Done in 9 admissions- 6 were negative, 1 grew pseudomonas, 1 grew klebsiella, and 1 grew contaminant

ASOT- Done in 2 admissions- Negative

Viral studies- Done in 3 admissions- 1 case- not reported. 2 admissions- IgM for rubella and measles negative.

Monospot- Done in 2 cases- Negative

Ultrasound scan- neck- Done in 1 case- Multiple lymph nodes, more on the left side of neck.

CXR- Done in 2 cases- Normal (figure 3).

Table 2: ECHO reports

CASE SERIAL NUMBER	ECHO REPORTS (FIRST/FOLLOW-UP)	REMARKS IF ANY
1	Appointment given	Did not attend
2	Nil significant abnormalities	
3	No aneurysm. LMCA (Left main coronary artery) 2.2 mm	
4	Nil significant abnormalities	
5	Nil significant abnormalities	
6	Nil significant abnormalities-? Small PDA(patent ductus arteriosus)	
7	LMCA(Left main coronary artery) prominent	
8	Mild pericardial effusion.? Aneurysm of proximal RCA(right coronary artery)- 4mm, increased density around LAD (Left anterior descending)	
9	Nil significant abnormalities	
10	Mild dilated coronaries- 2-3 mm	
11	LCA mildly dilated-3.1 mm.RCA-1.9 mm. Referred to RH for urgent ECHO, which was normal	-11 week ECHO ?abnormal. Subsequent ECHO normal
12	Not in records	Treated. Left against medical advice.
13	Some dilatation of coronaries. Referred to RH(Royal hospital, Muscat)	
14	Some brightness of Coronaries-RCA 1mm, LCA(Left coronary artery) 1.6 mm.	
15	Coronary Arterial dilatation with bright RCA walls. Referred to RH	
16	LCA 1.9 mm, more prominent. Bright walls of both coronaries	
17	-	Advised ECHO. No ECHO report in records.
18	Nil significant abnormalities	

ECHO reports

The ECHO was abnormal in 8 children. Not done yet in 3 children, and reported normal in 7 children. 3 children are awaiting follow-up ECHO appointments at Royal Hospital at the time of this study (table 2).

Diagnosis and treatment

For classic KD, the diagnostic criteria require the presence of fever for at least 4 days and at least four of five of the other principal characteristics of the illness. In atypical or incomplete KD, patients have persistent fever but fewer than four of the five characteristics. In these patients, laboratory and echocardiographic data can assist in the diagnosis.

Three of the 18 admissions (16.7%) fit in with the diagnostic criteria for typical Kawasaki disease. 13 admissions (72.2%) conform to a diagnosis of suspected incomplete Kawasaki disease. In the remaining 2 admissions (11.1%), there is insufficient data documented to diagnose Kawasaki disease. All cases were given the recommended treatment of IVIG in the dose of 2 g/Kg . 2 cases were given a 2nd dose of IVIG. Aspirin was started in all cases at a dose of 80- 100 mg/ kg/ day initially, tapered to 3-5 mg/ kg/ day after 2 weeks or fall in ESR, signifying fall in inflammation.

In one case (one of the two youngest children in this study-a 4 month old boy with incomplete Kawasaki disease), methyl prednisolone in the dose of 30 mg/ kg/ day IV was given for 2 days, following non response to 2 doses of IVIG .

DISCUSSION

KD occurs worldwide, with the highest incidence in Japan, and it most often affects boys and younger children. Approximately 1% of patients who recover from acute Kawasaki disease will develop giant coronary artery aneurysms or coronary artery obstruction due to thrombosis or stenosis. In most patients coronary ectasia or aneurysms regress within 1 to 2 years.

In our retrospective study, we looked at epidemiological data, clinical presentation, investigations, ECHO reports, diagnosis and treatment.

Epidemiological data

KD mostly presents in under-fives. In our study also, most admissions were aged under 5, with the age range being 4 months- 7 years. Majority were boys from North Batinah region, who stayed in hospital for an average time of 5.5 days, and mostly presented in the first half of the year.

Clinical presentation

Of the added criteria for diagnosis (fever being the common criteria in all), oral mucosal changes were

noted the most, and extremity changes the least. There were also some additional non-specific symptoms noted.

Investigations

Most children had a significantly raised platelet count. CRP was raised in all cases where it was done. Many children had a drop in their Hb levels. A range of other investigations done included WCC, ESR, Albumin, ALT, blood and urine cultures, Urine microscopy, and CXR, ASOT, viral studies, Monospot, Ultrasound of the neck. This may reflect the variable presentation of the disease with time, and the range of possible differential diagnoses.

ECHO

53% children who had ECHOs done had some abnormality in the first and/or follow-up ECHOs. These include coronary artery brightness/ prominence, dilatation, and pericardial effusion. This favours the use of ECHO not just to aid the diagnosis of atypical cases, but also to identify the children who need follow up.

Diagnosis and treatment

72% were diagnosed and treated as incomplete KD. This points to heightened clinical awareness of the atypical presentation of the disease. All the children were given and responded to standard treatment. 5.5% of admissions (1 child) needed 2nd line drug- methyl prednisolone.

Limitations

This was a retrospective study, and hence relied on hospital records. This underlines the importance of specific, detailed documentation.

Future research

It definitely is an area for useful clinical research in Paediatrics in the region, as in the rest of the world.

CONCLUSIONS

This study outlines the clinical presentation, diagnosis, treatment and awareness of KD in a part of Oman. This may form the basis of future prospective studies, perhaps in a larger population in the region. KD is evolving into a definite, identifiable clinical entity in children, with preventable, far-reaching clinical consequences.

ACKNOWLEDGEMENTS

ABBREVIATIONS
KD- Kawasaki disease
WCC- White cell count
CRP- C reactive protein
ESR- Erythrocyte sedimentation rate
HPF- High power field
ALT- Alanine amino transferase
AST- Aspartate amino transferase
IVIG- Intravenous immunoglobulin
ECHO- Echocardiogram
Hb- Haemoglobin
RA factor- Rheumatoid factor
ASO titre- Anti-streptolysin O titre
ANA- Anti nuclear antibody
EBV serology- Ebstein Barr Virus serology
CSF – Cerebrospinal fluid

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