Kawasaki disease, Atypical presentation in Saudi Arabia: A Trend

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Kawasaki disease: Atypical vs incomplete
• The first case of KD was recognized in Japan 1961

• Cases of sudden death more recognized in 1970 with autopsy findings showing CA aneurysms and thrombosis
• The annual incidence (< 5 years of age):
  • 70-80 cases/ 100,000 children (Japan)
  • 7-8 /100,000 (USA)
  • ?? (KSA)

• In epidemic years, may increase about 6 folds
• The peak age of onset: 1 year of age
  (80-85% of cases < 5 years of age)
Kawasaki Disease

Unique in several respects:

- Acute febrile self limited illness
- Multi-system vasculitis
- Diagnosed by clinical criteria
- Not necessarily a benign disease
- Mostly in children younger than 5 years of age
KD is one of the most thoroughly investigated inflammatory disorders

Questions remain unanswered:

• Etiology of KD
• Reason that IVIG is an effective therapy
• Variable susceptibility of different populations to the disease and its sequelae
Diagnosis of KD

A major impediment: absence of a “gold standard” for defining the condition!

• Still no diagnostic test for KD
• Diagnosis rely upon the same criteria that proposed 45 years ago
Classification Criteria for KD
The American classification Criteria for Kawasaki Disease

Fever $\geq$ 5 days plus at least FOUR of the following clinical signs not explained by another disease process:

1. Bilateral conjunctival injection
2. Changes in the oropharyngeal mucous membranes (including one or more of: injected or fissured lips, strawberry tongue, injected pharynx)
3. Changes in the peripheral extremities, including erythema or edema of the hands and feet (acute phase) or periungual desquamation (convalescent phase)
4. Polymorphous rash, primarily truncal; non-vesicular
5. Cervical lymphadenopathy with at least one node $>$ 1.5 cm

Modified from Centers for Disease Control: revised diagnostic criteria for Kawasaki disease MMWR 1990; 39
Japanese Classification Criteria for Kawasaki Disease

The presence of 5 of the following 6 criteria:

1. Fever
2. Bilateral conjunctivitis
3. Changes of lips and oral cavity
4. Changes in the peripheral extremities
5. Polymorphous rash
6. Cervical lymphadenopathy

Diagnostic guidelines for Kawasaki disease 2002
• Dr. Kawasaki proposed criteria in response to a controversy about whether KD truly represented a condition different from SJS and erythema multiforme

• Cardiac involvement in KD largely resolved this controversy
Another controversy!!

- Did children with CAA necessarily have KD?
- With few exceptions, (CAA may occur in So-JIA, SLE, PAN): the answer seems to be positive

- It is not known whether children with viral or febrile illnesses might develop transient CAA during their disease course!
• CAA are generally regarded as confirmation of a diagnosis of KD if there is no evidence of another inflammatory disease.

• This provide a convincing marker of KD in 25% of children who develop CAA, but leaves the reminder at the mercy of subjective diagnostic criteria and clinical impressions.
Classification Criteria for Kawasaki Disease

Fever persisting $\geq$ 5 days (mandatory criterion) plus 4 of the following 5 features:

1. Bilateral conjunctival injection
2. Changes in the oropharyngeal mucous membranes
3. Changes in the peripheral extremities or perineal area
4. Polymorphous rash
5. Cervical lymphadenopathy

In the presence of coronary artery involvement (detected on echo) and fever, fewer than 4 of the remaining 5 criteria are sufficient.

*Ann Rheum Dis 2006; 65*
Case 1

- A previously healthy 3 old girl, presented with
  - 10 days history of fever
  - Bilateral conjunctivitis with severe photophobia
  - Erythematous rash
  - Dry, caked lips and erythematous pharynx
  - WBC 8.3, Plat 331, ESR 110
  - Echo: 6 mm dilatation of L main coronary artery
- IVIG and Aspirin
- 2 wks follow up: desquamation of fingers and toes
- Repeated Echo: regression in CAA
Case 2

- A 6 year old boy presented with 3 weeks history
  - Fever
  - Conjunctivitis
  - Hyperemic oral mucosa and carked lips
  - Erythematous rash
  - Edema of both hands and feet
  - Wbc 19.3, Plat 540, ESR 127
  - Echo: pericardial effusion but No CAA

- IVIG and Aspirin: improvement
Case 2  cont..

• A few days later fever and rash reappeared
• A recurrent KD was suspected: retreated IVIG
• Patient’s condition deteriorated
  - Pancytopenia,
  - ESR 110,
  - AST 294, ALT 375, Albumin 24, Total bilirubin 724,
  - Septic work up: negative
  - Viral screening: negative
  - Repeated Echo: LCAA, otherwise normal heart
  - Triglyceride 3.4, serum ferritin 29400, LDH 4640
Case 2  cont..

- BMA: hypocellular marrow
- Abdominal CT: focal hepatic lesions
- Liver biopsy: hemaophagocytic cells

• Final diagnosis: Hemophagocytosis complicating KD
• Well response to High dose of prednisone and VP16
Nomenclature and definitions: pitfalls and confusion

Atypical VS incomplete
• AHA and AAP recommend that the phrase ‘atypical KD’ be reserved for patients who have clinical manifestations e.g. “renal impairment” that generally is not seen in KD

• Incomplete KD should be considered in all children with prolonged unexplained fever associated with less than the required criteria

  *Pediatrics 2004*

• A single patient with CAA might at the same time have both “incomplete” and “atypical” if he/she shows less than required criteria, accompanied by unusual features!!
Early reports suggested high mortality rate among children with atypical or incomplete KD

- Requirement of CA abnormalities if there are less than the required clinical criteria
- Diagnostic delays are more common if:
  - the phenotype is not typical
  - Concomitant infection
- Delayed treatment
- The younger patients are less likely to demonstrate full criteria and more likely to have CAA
Infections and KD
Many infectious agents have been associated with the onset of KD
Infectious agents and KD

- 129 consecutive patients with KD seen at HSC
- 33% of the patients had 1 confirmed infection
  (otitis 23%, strep throat 21%, viral infections 18%, pneumonia 8%, other 9%)

Infection may co-exist with KD
Trigger KD

- Other patients had no confirmed infection
- The presence of infection did not alter the response to treatment with IVIG (83%)

*Pediatrics 116; 2005*
Infectious agents and KD

- 31% of the patients developed CAA.
- Both the proven-infection and no-proven-infection groups had a similar CAA frequency.
- Proven infection did not increase the risk of CAA even after adjusting for other factors impacting on CA outcomes.

*Pediatrics 116; 2005*
• Patients with concomitant viral infections had a higher frequency of CAA and were significantly more often diagnosed with incomplete KD (delayed diagnosis!)

• The presence of a concomitant viral infection should not exclude the diagnosis of KD

Pediatr Infect Dis J 2010, 29
Many researchers now believe that KD represents a final common pathway of immune-mediated vascular inflammation in genetically susceptible individual triggered by infections.
Kawasaki Disease

It is a clinical diagnosis

No Specific lab results

- Increased acute phase proteins
- Increased WBCs, Platelets
- Increased LFT, bilirubin
- Decreased albumin
Cardiac Involvement

Coronary artery abnormalities

Congestive heart failure as result of:

- myocarditis, myocardial infarction

Pericarditis

Arrhythmia
• Without a ‘gold standard’ for diagnosing KD, no clinical criteria have a high enough positive predictive value to ensure treatment decisions

• Whether to give or not give IVIG in doubtful cases is still a difficult decision, and expert opinion will be required until more specific diagnostic markers are identified
Severity/ Risk Scoring Systems

To identify children at highest risk for CAA

- White cell count > 12,000
- Platelet count < 350,000
- Serum CRP > 5.0 mg/L
- Hematocrit < 35%
- Serum albumin < 3.5 g/L
- Male gender
- Age either <12 months, ≥ 5 years

Acta Pediatr Jpn 1991; 33
Pediatrics 1995; 95
Risk Scoring Systems

Imperfect performance scoring systems

_Circulation_ 2004, 110
High Risk Group

- Duration of fever
- Infants <6 months
- Children >8 years
- High CRP, LDH, ALT, Bilirubin?
Treatment

• The major goal of treatment is to prevent serious cardiovascular manifestations of KD

• Early recognition

• Prompt institution of appropriate treatment
Intravenous Immunoglobulin

- 2 meta-analyses have demonstrated a dose-response effect
- A single infusion (2g/kg) having the greatest efficacy
- Approximately 80-90% of children respond
- Reduces the incidence of CAA by 80%
- Remainder may continue to have persistent or recrudescent fever and other symptom

*Pediatrics 1995, 96*
*J Pediatr 1997, 131*
Treatment: IVIG

- It should be instituted within the first 10 days of illness.
- Treatment before day 5 of illness appears no more likely to prevent cardiac sequelae than does Rx on days 5-7

*J Pediatr* 2004, 144
*Pediatr Cardiol* 2004, 25
Treatment: IVIG after 10 days of illness

- Treatment should be given to patients if they have:
  - persistent fever
  - aneurysms and ongoing systemic inflammation, as manifested by elevated ESR, CRP

_Circulation 2004, 110_
Aspirin

- Will not prevent/reduce the incidence of CAA
- Dose 80-100 VS 30 mg/ kg/ day

*Pediatrics 2004; 114*

**Aspirin in patients without CAA:**
- Change to low dose, once the acute inflammation resolves
- D/C when all lab values normalized (6-8 weeks)
Aspirin: long term

- Patients with CAA: Should continued until normalisation of aneurysms is noted

- In children with aspirin intolerance, another anti-platelet agent may be used to prevent the formation of thrombi such as dipyridamole (2-3 mg/kg).

- In patients with giant aneurysms the addition of warfarin to aspirin has been suggested
Corticosteroids
Indications and the efficacy of Corticosteroids in KD

- 26 patients (81%) with persistent fever despite treatment with IVIG (refractory KD), 5 patients (19%) for congestive heart failure
- 22/26 (85%) had rapid, sustained resolution of fever after corticosteroids
- 8 patients (31%) treated with corticosteroids developed CAA
- 4 had aneurysms detected prior to corticosteroids.
- Corticosteroids are effective in the treatment of fever in most patients with IVIG-refractory KD

*J Rheumatol. 2006; 33*
Corticosteroids

Meta-analysis of 8 studies (862 pts):

A significant reduction in the incidence of CAA among patients who received steroid therapy plus ASA +/- IVIG compared with ASA +/- IVIG alone

The inclusion of corticosteroids in aspirin-containing regimens for the initial treatment of Kawasaki disease reduces the incidence of coronary aneurysms

*Pediatrics* 2005; 116
Corticosteroids as primary therapy of KD

Recent report does not provide support for the addition of a single pulsed steroid to conventional IVIG for the routine primary treatment of children with KD

It has beneficial effect in selected patients

N Engl J Med 2007; 356
Other Treatment

- Infliximab
- Pentoxifylline (Trental)
- Plasma exchange
- Abciximab
  (a monoclonal platelet glycoprotein IIb/IIIa receptor inhibitor)
- Cytotoxic (Cytoxan)
Other Treatment

- Used in small numbers of patients
- Controlled data are lacking
- The relative roles remain unclear
The effect of TNFalpha blockade (Infliximab) in complicated, refractory Kawasaki disease

In case report, the effect was prompt and long-lasting. Clinical improvement was seen within a few days after the first dose, and regression of the aneurysms occurred within weeks.

*Scand J Rheumatol. 2006; 35*

patients with IVIG-resistant Kawasaki disease whose first re-treatment was with infliximab, compared with IVIG, had faster resolution of fever and fewer days of hospitalization. Coronary artery outcomes and adverse events were similar.

*J Pediatr 2010*
Conclusion

• KD is not uncommon disease (underestimated !)
• It is a clinical diagnosis
• Needs high index of suspicion
• Prompt treatment