Fever & Cracked Lips: Is It Kawasaki?

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Overview

- Review of Kawasaki Disease characteristics
  - Clinical
  - Laboratory
- Epidemiology
- Incomplete KD
  - Diagnostic algorithm
- Therapy
- Late follow-up

Mucocutaneous Lymph Node Syndrome (Kawasaki, 1967)

Fever of > 101.3 °F persisting at least 5 days, no other diagnosis AND 4 of the 5 criteria:

1. Bilateral conjunctival injection
2. Erythema & cracking of lips, strawberry tongue, erythema of pharynx
3. Erythema & edema of hands and feet; later peeling
4. Polymorphous exanthem
5. Cervical lymphadenopathy (> 1.5 cm.), usually unilateral
Laboratory Findings

- Leukocytosis with neutrophilia
- Elevated erythrocyte sedimentation rate
- C-reactive protein > 3.0 mg/dL
- Anemia (normochromic, normocytic)
- Sterile pyuria
- Elevated transaminases
- Hypoalbuminemia
Who gets Kawasaki Disease?

Kawasaki affects the toddler - hospitalizations
Kawasaki affects males more than females

Race-Specific Incidence Estimates
(par 100,000 children age < 5 years)

- Japanese: 135
- Asian/Pacific Islanders: 33
- Blacks: 17
- Hispanic: 11
- Caucasians: 9

Holman et al, Pediatrics, 2003

What if it isn't typical Kawasaki?
What if it isn’t typical Kawasaki?

Kawasaki Disease in the 21st Century

- Need for new algorithm to decide when a child with incomplete signs of KD should be treated with IVIG
- Epidemiologic case definition should be separated from treatment criteria
- Strive for greatest sensitivity
- Maintain sufficient specificity to prevent wide-scale overuse of IVIG

Epidemiologic Case Definition of KD

- Fever of at least 4 days and ≥ 4 principal criteria, without other explanation
- Fever and < 4 principal criteria if coronary artery abnormalities detected by echocardiography or coronary angiography
Evaluation of Suspected Incomplete Kawasaki Disease

Fever ≥ 5 days and 2 or 3 clinical criteria

Assess Patient Characteristics

Consistent with KD

Assess Laboratory Tests

Laboratory tests for assessing incomplete Kawasaki Disease

- White blood cell count
- Hematocrit/hemoglobin
- C-reactive protein (CRP)
- Sedimentation rate (ESR)
- Albumin
- Platelet count
- Urinalysis (micro)
- Liver function tests.
Fever ≥ 5 days and 2 or 3 clinical criteria

Assess Patient Characteristics

Consistent with KD

Inconsistent with KD

Persistent Fevers

Assess Laboratory Tests

KD Unlikely

Patient Characteristics Suggesting Disease Other Than KD

- Exudative conjunctivitis
- Exudative pharyngitis
- Discrete intraoral lesions
- Bullous or vesicular rash
- Generalized adenopathy

Assess Laboratory Tests

CRP ≥ 3.0 mg/DL +/or ESR ≥ 40 mm/hr

< 3 Supplemental Laboratory Criteria

≥ 3 Supplemental Laboratory Criteria

Supplemental Laboratory Criteria

- Albumin ≤ 3.0 g/dL
- Anemia for age
- ↑ ALT
- Platelets after 7d ≥ 450K
- WBC ≥ 15K
- Urine micro ≥ 10 WBC/HPF
Assess Laboratory Tests

CRP ≥ 3.0 mg/DL +/or ESR ≥ 40 mm/hr

< 3 Supplemental Laboratory Criteria

≥ 3 Supplemental Laboratory Criteria

Echo

Criteria for “Echo +”: Any of the following 3 criteria

A. LAD or RCA Z score ≥ 2.5 or
B. Japanese Ministry of Health Criteria
   - CA diameter:
     - > 3 mm in children < 5 years
     - > 4 mm in children ≥ 5 y
   - Lumen diameter ≥ 1.5 X an adjacent segment
   - Coronary lumen is clearly irregular

Criteria for “Echo +” (Continued)

C. ≥ 3 suggestive features:
   - Peri-vascular brightness
   - Lack of tapering
   - ↓ LV function
   - Mitral regurgitation
   - Pericardial effusion
   - LAD or RCA Z score = 2 - 2.5
Advantages to New Algorithm

- Acknowledges the varied presentations of Kawasaki disease
  - Separates the epidemiologic case definition from treatment criteria
- Bases criteria for treatment, in part, on the risk of coronary aneurysms
- Lowers the likelihood of delay of effective treatment for children at risk
Success of 2004 AHA algorithm for IVIG treatment: tested in patients with KD and aneurysms (n=195)

- # with complete KD: 137 (70.3%)
- # without complete KD: 58 (29.7%)
- # treated according to algorithm: 53/58 (91.4%)
- Total # treated correctly: 190/195 (97%)

Yellen et al. Pediatrics 2010

Infants ≤ 6 Months Old

Have highest incidence of
- Coronary aneurysms
- Atypical or incomplete disease

If fever lasts ≥ 7 days without other explanation but with laboratory measures of inflammation, even in the absence of any principal clinical criteria, obtain ECHO

Treatment of KD
Recommended Kawasaki Disease Therapy During the Acute Phase

Intravenous Gamma Globulin
2 g/kg over 8 - 12 hours

*Plus*

Aspirin
80 mg/kg/day until afebrile,
then 3 - 5 mg/kg QD

Retreatment with IVIG

- Approximately 10-15% of children have recrudescent or persistent fever ≥48 hours after IVIG
- "Standard practice" is to retreat if patient has persistent or recrudescent fever more than 36 hours after completion of first IVIG infusion
- Usual retreatment dose is 2 g/kg
Potential mechanisms of action of IVIG

- Blockade of Fc receptors
- Induction of Fc gamma IIR with crosslinking of Fc gammaII/IIIR leading to down-regulation of cell activation
- Provision of anti-agent, anti-toxin, anti-cytokine, or anti-idiotype antibody
- Blockade of NK cell/vessel wall interaction
- Prevention of complement fragment binding to target cell (eg. endothelium)

Other Therapies

- Steroids (primary and rescue)
- Infliximab TNFalpha ab (rescue)
- Abciximab gIIb/IIIa inhibitor (aneurysm regression)
- Cytotoxic agents cyclophosphamide (rescue)
- Plasmapheresis (rescue)
Antithrombotic Therapy

- Aspirin
- Clopidogrel (Plavix)
- Warfarin (Coumadin)
- Low molecular weight heparin

Coronary aneurysms

[Diagram showing coronary artery anatomy with percentages labeled: RCA 77.6%, LMT 11.6%, LAD 87.6%, LCX 25.9%]
Coronary Artery Aneurysms

Risk Factors for Aneurysms:

- Male gender
- Young (< 1 yr) or old (> 5 yrs) age
- Persistent fever despite IVIG
- Labs at presentation
  - Low Hct or Hgb
  - Low platelet count
  - Low Albumin
  - High CRP
  - Higher absolute band count
- More disease criteria
At 9 months, bifurcation of LMCA measured 8 mm.
At 15 years, maximum IMT at bifurcation was 2.2 mm.

Tsuda et al, Peds Cardiol 2002
Treatment of Coronary Thrombosis

- Thrombolytic therapy
- Platelet Glycoprotein llb/llla receptor antagonists, with ½ dose thrombolytic therapy
- Transcatheter coronary intervention for mechanical restoration of coronary blood flow
Myocardial Infarction in Kawasaki Disease:
Interval from the onset of KD

![Graph showing interval from onset of KD to myocardial infarction]

(Kato H, Ichinose E: J Pediatr, 1985)

Indications: Catheter Intervention*

- Ischemic symptoms, or
- Reversible ischemia on stress test, or
- ≥ 75% stenosis in LAD.
- Bypass surgery preferred in pts with severe LV dysfunction.
- Contraindicated for multiple, ostial, or long-segment lesions.


Once coronary disease occurs, it is treated with the usual tools of the adult cardiologist (PTCA, stents, CABG, transplantation, etc.).

Prevention is better than treatment.
Kawasaki Disease Without CAA:
Natural History

- No late clinical manifestations with ~25 years of follow-up (Kato)
- However:
  - Abnormal lipid metabolism (lower HDL, higher TGs)
  - Significantly lower myocardial blood flow and coronary flow reserve with adenosine (Muzik et al, JACC 1996)
  - Higher pulse wave velocity, suggesting increased arterial stiffness (Cheung JACC 2004, Ooyanagi Peds Int'l 2004)
  - Abnormal myocardial biopsies

Coronary artery disease risk factor reduction

- Encourage exercise (avoid sedentary lifestyle)
- Heart-healthy diet
- Treat hyperlipidemia
- Treat hypertension
- Never start smoking
- Consider KD patients as primary vs secondary prevention?

The Future

- Discover the cause(s) of Kawasaki disease
- Block critical pathogenic mechanism(s)
- Identify the vulnerable host (genetics)
- Multi-center trials and registries to assess existing and new therapies.
Summary

- Untreated Kawasaki Disease can be associated with coronary findings, therefore diagnosis is key
- Incomplete Kawasaki Disease can be diagnosed using a published algorithm
- Aneurysms can regress
- Patients with history of KD, even without history of aneurysms, have no symptoms, but signs of increased CVD risk