Kawasaki Disease: An Update

Mary Beth Son, MD
Boston Children’s Hospital
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No disclosures relevant to this talk
Outline of Talk

• Signs and Symptoms of KD
• Diagnosis
• Treatment – knowns and unknowns
• Long Term Prognosis/Outcomes

History: Kawasaki Disease

• 1967: Dr. Tomisako Kawasaki, a Japanese pediatrician, describes “mucocutaneous lymph node syndrome”
  – Thought that the illness self-resolved without intervention and had no sequelae
• Rapid increase in incidence of KD form 1960’s-1080’s with continued increasing prevalence
Original Diagnostic Criteria

Fever of $> 101.3 \, ^\circ\, F$ persisting at least 5 days AND 4/5 following criteria:

- Bilateral conjunctival injection
- Erythema & cracking of lips; strawberry tongue & erythema of pharynx
- Erythema & edema of hands and feet; later peeling
- Polymorphous exanthem
- Cervical lymphadenopathy ($> 1.5\, cm.$), usually unilateral

Epidemiologic Case Definition

• In the presence of fever and $\geq 4$ principal criteria, the diagnosis of KD can be made on Day 4 of illness.

• Patients with fever and $< 4$ principal criteria can be diagnosed with KD when coronary artery abnormalities are detected on imaging (usually echocardiogram).
Recurrent KD?

- Japan: ~3% recurrence rate, highest risk in the 2 years following index case
  – Higher risk of developing coronary artery sequelae with recurrence.

- US: Overall rate of recurrence is 1.7% with 3.5% in Asians and Pacific Islanders

doi: 10.1111/ped.12733
Signs of Kawasaki Disease

Other Clinical Manifestations

**Respiratory**
- Peribronchial/Interstitial Infiltrates
- Pulmonary nodules

**Musculoskeletal**
- Arthritis/Arthralgia

**Gastrointestinal**
- Diarrhea, vomiting, abdominal pain
- Hepatitis
- Hydrops of the gallbladder
- Pancreatitis
Other Clinical Manifestations

**Neurologic**
- Irritability
- Aseptic meningitis
- Facial nerve paresis
- Sensorineural hearing loss

**Genitourinary**
- Urethritis
- Hydrocele

Differential Diagnosis

- Measles
- Adenovirus/Enterovirus
- Staph/Strep toxin mediated diseases
- Drug hypersensitivity reaction
- Systemic onset juvenile idiopathic arthritis
- Rocky mountain spotted fever (rickettsial)
- Leptospirosis
Characteristics Suggesting Disease Other Than KD

- Exudative conjunctivitis
- Exudative pharyngitis
- Discrete intraoral lesions
- Bullous or vesicular rash
- Generalized adenopathy
The Thing To Remember: Infants ≤ 6 Months Old

- Have highest incidence of
  - Coronary aneurysms.
  - Atypical or incomplete disease.
- Echo if fever ≥ 7 days without other explanation and with laboratory measures of inflammation, *even in the absence of any principal clinical criteria.*
Number of Clinical Criteria Among Patients with Coronary Artery Aneurysms

What Causes Kawasaki Disease?
Race-Specific Incidence Estimates

*(per 100,000 children age < 5 years)*

- Japanese (in Japan) 264
- Asian/Pacific Islanders 33
- Blacks 17
- Hispanic 11
- Caucasians 9
Evidence from Japan that KD has a Genetic Component

• Siblings have an ~ 10-fold relative risk

• Emerging recognition of KD in successive generations

Signaling Pathways Participating in KD Pathogenesis

• Calcineurin-NFAT (ITPKC), contributes to susceptibility to KD and to CAL
  – Treatment with calcineurin inhibitors?

• TGFβ - SNPs in TGFβ2, TGFβR2, and SMAD3 contribute to risks of CAL
  – Treatment with statins?

• FCGR2A (encoding FcγRIIa), contributes to disease susceptibility
Tropospheric Wind Patterns Are Associated with Incidence of KD

KD and surface winds in Japan (a), San Diego (b) and Hawaii (c).

Rodo X et al., Sci Rep 2011

Tropospheric Winds

- Are aerosolized particles from Central Asia the culprit of KD?
- Deep sequencing of the tropospheric biome has disclosed Candida species
Goals for Therapy in the Acute Phase

- Reduce the systemic inflammatory response
- Prevent coronary aneurysms - ideal
- If aneurysms already present:
  - Minimize peak dimension reached
  - Prevent coronary thrombosis
Recommendations for Initial Treatment with IVIG and ASA

- IVIG (2g/kg) as a single infusion within 10th day of illness, as soon as possible after diagnosis
- It is reasonable to treat after the 10th day of illness with persistence of fever or coronary artery abnormalities with elevation of ESR or CRP (>3.0 mg/dl)
- Administer moderate (30-50mg/kg/d) to high-dose (80-100mg/kg/d) ASA until patient is afebrile

Rescue Therapy After First IVIG

Given to high-risk patients:
- IVIG resistance/fever
  - Defined as recrudescent or persistent fever ≥36 hours after end of IVIG
- Evolving coronary aneurysms
- Options: 2nd dose of IVIG, steroids, infliximab

McCrindle et al. Circulation. 2017;135(17)
IVIG can be associated with antibody-mediated hemolytic anemia especially patients with non-0 blood groups who have:
- High doses of IVIG
- High degree of inflammation.

Intravenous immunoglobulin-related hemolysis in patients treated for Kawasaki disease.
Children's National Medical Center, Washington, DC.
George Washington University School of Medicine and Health Sciences, Washington, DC.

Efficacy of IVIG + Prednisolone in IVIG-Resistant Patients
Kobayashi et al, J. Pediatr 2013

- Failure to respond to first-line rescue therapy
- CAA < 1 mo
- CAA at 1 mo
Consider Primary Adjunctive Treatment In High-Risk Patients

- High Kobayashi score in Japanese children
- Dilated coronary arteries at baseline
  - Baseline zMax ≥2.0 has C statistic of 0.77, sensitivity = 80%, and negative PV = 98%
- Age <6 mo: Among those dxed ≤10 days
  - 43% with CAA or dilation at baseline
  - 19% with normal CAs at baseline develop CAA

Son JAHa 2017; Tremoulet J Pediatr 2017
Randomized Trial of Pulsed Corticosteroid Therapy for Primary Treatment of Kawasaki Disease


Primary Outcome: largest z score (LAD or RCA) at Week 5

Secondary Outcomes: Hospital days, days of fever, IVIG resistance

NEGATIVE STUDY

Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial

Tooru Kobayashi, Tsutomu Saji, Tetsumi Otsun, Kazuo Takahashi, Tetsuya Nohara, Hirunori Arakawa, Tsuichi Kato, Toshiro Haru, Kenji Hamada, Shizuyuki Ogasawara, Masaru Mimura, Yuichi Nomura, Shigeo Furue, Fumiko Ikeda, Mitsuru Seki, Ryuzi Ukita, Chitose Ogawa, Kenji Furuno, Hiroshi Fukunaga, Shinichiro Takatsuki, Shinya Han, Akihito Morikawa, on behalf of the RAISE study group investigators

- Primary Outcome: incidence of coronary artery abnormalities during study period (through Week 4 of illness; measurements at Weeks 1, 2 and 4)

- Secondary Outcomes: Incidence of CAA at Week 4, z scores, need for rescue treatment, days of fever, CRP at Weeks 1 and 2, and SAE

MET ALL OUTCOMES
Generalizability of RAISE?

- Well established risk score utilized in study
- Early diagnosis
- Fairly long hospitalizations for IV prednisolone treatment
- Questions remain regarding duration/dose/type of steroid
“High risk patients with KD benefit greatly from a timely and potent adjunctive corticosteroid therapy.”

Criticisms: 6 studies, 383 patients and only 167 treated with steroids and in varying regimens, not applicable to all populations

Infliximab 1° Treatment Trial
Tremoulet et al., Lancet 2014

- 196 patients randomized to infliximab vs. placebo, plus conventional therapy.
- No measurable effect on treatment resistance (11% in both groups)
- Infliximab group had significantly better
  - Laboratory measures of inflammation
  - Fewer days of fever after treatment
  - LAD z at 2 weeks (borderline)
- No significant difference in CAA or coronary z scores at 5 weeks.
Classification of Coronary Artery Abnormalities

<table>
<thead>
<tr>
<th>Classification</th>
<th>Size of Coronary Artery Abnormality</th>
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<tbody>
<tr>
<td>No coronary involvement</td>
<td>Z-score always &lt; 2</td>
</tr>
<tr>
<td>Dilation only</td>
<td>Z-score 2 to &lt;2.5</td>
</tr>
<tr>
<td>Small aneurysm</td>
<td>Z score ≥ 2.5 to &lt;5</td>
</tr>
<tr>
<td>Medium aneurysm</td>
<td>Z score ≥5 to &lt;10</td>
</tr>
<tr>
<td>Large or giant aneurysm</td>
<td>Z score ≥10 or absolute dimension of ≥8 mm</td>
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What happens to aneurysms?

- All had coronary angiography, 146 patients had aneurysms (25%)
- Nearly 50% had regression at 1-2 years
- Ischemic heart disease in ~5%, MI in ~2%

Regressed Aneurysms

- Luminal myofibroblastic proliferation
- Abnormal coronary reactivity to nitrates
- Abnormal endothelial cell function
- Decreased myocardial blood flow and coronary flow reserve

Myocardial Infarction in Kawasaki Disease

Interval from the onset of KD


Asymptomatic
Symptomatic
Survival After Myocardial Infarction

Kaplan-Meier survival curve of the entire cohort of patients with giant coronary aneurysms.
Survival and Cardiac Event Free Rates

VT-Free Survival After Myocardial Infarction

Tsuda E, American Heart Journal, 2014

Tsuda et al. Pediatric Cardiology 2011
Most Data Are Reassuring for the KD Patient Whose Coronary Arteries Were Always Normal

- No late clinical manifestations with ~40 years of follow-up, and no increase in standardized mortality ratio.

• Adults < 40 who underwent coronary angiograms for suspected myocardial ischemia at 4 San Diego hospitals (n=261)

• Of 261, 16 had coronary artery aneurysms

• 4 had a known history of KD, 9 had presumed KD
  • Paucity of traditional CAD risk factors, younger age, higher risk race for KD

• ~5% of young adults evaluated by angiography had coronary sequelae of KD.

• Lesions are different from typical atherosclerotic disease

Summary: Acute Management

• Reduce systemic and tissue level inflammation as rapidly as possible

• Treatment with IVIG should be given to
  − All patients on ≤ Day 10 of illness
  − Patients > Day 10 with fever or coronary enlargement with persistent inflammation.

• Rescue therapy should be given to patients with fever 36 h post completion of IVIG infusion, without other explanation.
  − IVIG-hemolysis in non-blood group O patients
Summary: Acute Management

- First choice for rescue therapies are IVIG ± steroids (RAISE regimen) or infliximab
- Rescue therapy with CSA and cytotoxic agents is generally used in patients in whom CAA are developing
- High-risk cases identified at baseline can be treated with primary adjunctive therapies in addition to IVIG.

Summary: Long-Term Management

- Pts without CA dilation during first weeks of illness have normal cardiovascular status.
- Remodeling of aneurysms is accompanied by luminal myofibroblastic proliferation and abnormal arterial function.
- Those with past or current aneurysms have life-long risk of progressive CA stenosis or occlusion and worsening ischemia.
- Long-term cardiovascular surveillance tailored to initial severity of disease and current coronary status