Kawasaki Disease: History and Clinical Practice

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One Night on Call.....

Your team is on call at Avera Children's Hospital, cross-covering the 2 y.o. girl on the 3rd floor, admitted yesterday with Kawasaki Disease. The evening nurse calls to report that the patient just vomited today's 4th aspirin dose. “Do we have to repeat the dose?” Later, the night nurse calls to inform you that the IV has infiltrated...the patient has received 80% of the IVIG. “Do we have to restart the IV?”

Where did Kawasaki Disease come from?
Pre-1960’s = Periarteritis Nodosa

- First diagnosis in 1866 – Kussmaul & Maier found arterial dilatation w/ transmural inflammation = “periarteritis nodosa” (PN) in adults
- Keith & Baggenstoss (1941) and others – pediatric PN cases had a more consistent coronary focus
- Pediatric cases of periarteritis nodosa increasingly reported, generally with autopsy diagnosis, in 1940’s and 1950’s.
- 1950’s – emerging consensus that pediatric PN was distinct, and “a constant clinical syndrome”

1960’s: first MCOS

- Itoga & Yamagishi 1960 published report of non-fatal “mucocutaneous ocular syndrome,”
- 20 cases – all treated with steroids.
- All cases between 2 months and 7 yrs. of age
- They believed it to be a variant of Stevens-Johnson Syndrome.

Tomisaku Kawasaki...in the beginning

- Born in 1925, the youngest of seven children
- “I was very interested in plants and fruit....I wanted to continue studying mutation.”
- “My mother wanted me to become a doctor.”
- Enrolled in Chiba Medical School
- “Adult patients were full of complaints, but sick children said little. Basically, I liked children.”
Emergence of A New Entity 1961-67

Dr. Tomisaku Kawasaki

Acute Febrile Mucocutaneous Lymph Node Syndrome

- Saw first case in 1961
- Presentation to a skeptical Japanese Pediatric Society (Chiba)
- 1964 at Central Japan Ped. mtg labeled them MCOS
- 1967 abandoned MCOS, emphasized cervical adenopathy (68%)  

Kawasaki's Assertions:

- The entity MCLS is distinct from MCOS, emphasized adenopathy.
- The constellation of findings are unrelated to Steven's-Johnson Syndrome.
- The syndrome is benign and self-limited.
- The cardiac abnormalities observed in similar patients are not related to MCLS.

Early 1970’s: Defining MCLS

- Japan MCLS Research Committee creates 1st case definition. Designed to detect those with the syndrome of Kawasaki, not to detect those at risk of coronary aneurysms.
- Original (1972) definition did not include cervical adenopathy, later (1974) did.
- First US cases in Hawaii, first by autopsy cases, then clinical cases (Melish and Hicks, 1974)

Late 1970’s: Unifying Clinical Concepts

- U. Hawaii pediatrics resident David Morens -- to CDC
- Skepticism at CDC re new diagnostic entity
- Creates case definition for CDC surveillance, based on J.R.C.
- “Kawasaki Disease” -- term unifies MCOS, pediatric PN, MCLS

Kawasaki Disease: A Clinical Portrait

MCLS: Case Definition

**PRINCIPAL DIAGNOSTIC CRITERIA**

1. Fever, persisting for more than 5 days
2. Conjunctival injection
3. Changes in the mouth consisting of:
   A. Erythema, fissuring and crusting of the lips
   B. Diffuse oropharyngeal erythema
   C. Strawberry tongue
4. Changes in the peripheral extremities consisting of:
   A. Induration of hands and feet
   B. Erythema of palms and soles
   C. Desquamation of finger and toe tips approximately 2 weeks from onset
   D. Transverse grooves across fingernails 2-3 months after onset
5. Erythematous rash
6. Enlarged lymph node mass measuring greater than 1.5 cm in diameter
Rash may be Morbilliform

Age Distribution of Kawasaki Disease

Fig 1. Kawasaki disease rates (age-adjusted, 1977 census estimates) by patient’s age at onset, United States, July 1, 1976 to June 30, 1978.

1970’s: Steroids and Aspirin

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Incidence of Coronary Aneurysm (%)</th>
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</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>15/77</td>
</tr>
<tr>
<td>Prednisolone plus salicylates</td>
<td>3/7</td>
</tr>
<tr>
<td>Prednisolone plus aspirin</td>
<td>0/7</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4/26</td>
</tr>
<tr>
<td>Antibiotic only</td>
<td>5/95</td>
</tr>
</tbody>
</table>

Treatment Consensus – late 1970’s

- Rheumatologic opinion favored high dose aspirin for anti-inflammatory effect
- Hematologic opinion favored low dose aspirin for antithrombotic effect on platelets
- Conclusion: high-dose ASA during intense inflammatory period (2 weeks) and low-dose ASA during convalescence
- Steroids appear to be contraindicated
1978: Kawasaki Arrives

1978-1980
Disruption of Conceptual Clarity

• Todd et al (1978) describe “toxic-shock syndrome” in 3 boys, 4 girls with mucosal phage group 1 Staph aureus
• Report met with skepticism (Denver/USA) and rejection (N.E.J.M.), published in the Lancet
• Simultaneous reports of “Adult Kawasaki Disease” – more acute than pediatric Kawasaki Disease
• 1980–emergence of tampon association (Minn/Wisc)
• “Toxishaki?” (unpublished term)

Lessons of the Kawasaki Disease Story 1940-1980

• Lesson #1 -- Discoveries of new clinical constellations are often met with skepticism by the medical community.
• Lesson #2 -- Rigorous study of pathologic anatomy tends to clarify clinical confusion.
• Lesson #3 -- There may be “critical periods” to answer important therapeutic questions, after which “conventional wisdom” dictates care.
• Lesson #4 -- Listen to your mother.

Infants with Kawasaki Disease are Different than Older Children (1980)

• K.E. was a 6 mo. old girl with 3 weeks of high fever with minimal physical findings.
• Cardiovascular deterioration and death occurred at 3 weeks.
• Post-mortem exam revealed generalized vasculitis, including larger vessels, and myocardial/endocardial involvement
• Post-mortem conference debate: Kawasaki Disease = Periarteritis Nodosa?

Investigation of Clinical, Laboratory Findings of Kawasaki Disease

• Dr. Jane Burns, resident caring for patient KE, begins ID training and proposes studying dozens of clinical and lab parameters of Kawasaki Syndrome.
• Proposal is met with skepticism by Senior ID Fellow, who cautions that patient numbers may be insufficient to arrive at meaningful conclusions.
• Dr. Burns proceeds with study
**Outbreak -- An Important Clue?**

**KAWASAKI SYNDROME: ASSOCIATION WITH THE APPLICATION OF RUG SHAMPOO**

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**Outbreaks and Seasonality**

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**Living near a Body of Water -- Epidemiologic Factor?**

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**1980’s – Intravenous Gamma Globulin**

- Emergence of IVIG in the 1970’s led to successful treatment of ITP in 1981.
- Early 1980’s -- Furusho and Furukawa in Japan reported successful treatment of Kawasaki Disease with IVIG.
- U.S.A. investigators launched controlled national collaborative study, by 1986 showed dramatic reduction of coronary aneurysms with IVIG (~5%) vs. placebo (20+%)

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**IVIG Impact on Aneurysms**

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**Intravenous Gamma Globulin (cont.)**

- Original study used 400 mg/kg/day X 4 days
- New national collaborative study (1986 to 1991) compared 4-day IVIG course with 2000 mg/kg in a single dose
- Slight superiority and convenience of single dose therapy established it as the currently recommended regimen.
- Usual course is ~12 hours, sometimes with pre-medication.
IVIG – Late 1980’s: What are We Doing?

- The presumption of an undiscovered microbial etiology led to hypothesis that IVIG was neutralizing microbes or their toxins.
- Other investigators believed that IVIG played an immunoregulatory role, perhaps binding Fc receptors on inflammatory cells.
- Observed efficacy intensified study of inflammatory mediators in Kawasaki Syndrome

Kawasaki Syndrome: Infectious Etiology?

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>POSSIBLE CANDIDATES</th>
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<tbody>
<tr>
<td>BACTERIA</td>
<td>Staph aureus</td>
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<tr>
<td></td>
<td>Group A Strep</td>
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<tr>
<td></td>
<td>Coxiella burnetii</td>
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<td></td>
<td>Rickettsia conorii</td>
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<tr>
<td>RICKETSSIA</td>
<td>Retroviruses</td>
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<tr>
<td>VIRUSES</td>
<td>Parvoviruses</td>
</tr>
<tr>
<td>SPIROCHETES</td>
<td>Borrelia</td>
</tr>
<tr>
<td>ECTOPARASITES</td>
<td>Leptospira</td>
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<tr>
<td></td>
<td>Carpet mites</td>
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Another False Start...

- Dr. Jane Burns, leading Kawasaki Disease investigator, finds evidence of reverse transcriptase in supernatant fluid of lymphocyte cultures of KD patients.
- Hypothesis emerges of a T-8-tropic retrovirus
- Dr. Burns and other investigators are unable to reproduce results.

Kawasaki Disease in the 1990’S

- Universal adoption of IVIG single dose
- Aspirin use continues (high-dose X 2 weeks, followed by 6-8 weeks of low-dose); some question its necessity and its dosage.
- Continued debate over microbial etiology, including Staph aureus, but growing evidence of immunologic dysregulation as central
- Recognition of children with “Atypical” and “Incomplete” Kawasaki Syndrome.

Kawasaki Disease in the 21st Century

- Increasing reports of variants of Atypical or Incomplete Kawasaki Disease
- Increasing use of echocardiography in assessment of febrile young children who do not fulfill case definition
- All criteria are not created equal:
  - Fever (now 4 days) and conjunctival injection are still virtually 100%.
  - Adenopathy, extremity changes are weaker
Kawasaki Disease in the 21st Century

- Increasing focus on key clinical subsets: infants with KS, patients with incomplete KS, patients with aneurysms, patients with refractory KS.
- Increasing focus on genetic explanations for striking population differences worldwide, e.g. demonstration that genes for IL-4 and chemokine receptor 5 influence Kawasaki Disease susceptibility.

Refractory KS -- Case example

- 7-week old infant is admitted with Kawasaki Syndrome, lacking mucocutaneous features.
- IVIG therapy is not followed by resolution
- Fever is refractory to 2nd dose of IVIG...
- Fever is refractory to high dose methylprednisolone...
- Became afebrile after two doses of infliximab
- Peripheral gangrene had developed over prolonged, refractory course and giant aneurysms were demonstrated on ECHO

Some Immunologic Alterations in Kawasaki Syndrome

- T-cell imbalance during the acute phase
- Increased cytokine production
- Appearance of circulating antibodies to endothelial cells activated with IL-1, tumor necrosis factor-alpha, or interferon-gamma
- Adhesion of leukocytes to endothelial wall, infiltration of neutrophils & mononuclear cells

Tumor Necrosis Factor: Central Role?

Some Immunologic Alterations in Kawasaki Syndrome

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Contemporary Frontiers

- Exploring seasonality and potential environmental factors
- Searching for sensitive/specific markers of KS in blood, seeking more inclusive case definition
- Evaluating genetic factors in KS susceptibility
- Evaluating treatment options for refractory KS
- Establishing long-term follow-up of KS patients

Leading Centers for Kawasaki Disease Research

Japan Kawasaki Disease Research Center
Kawasaki Disease Research Center - UC San Diego
Back to the Night on Call on 3rd Floor

• “Do we need to repeat the dose of aspirin that the patient vomited?”

• “Do we need to restart the IVIG if he has received 80% of the dose?”

• Final lesson – the rationality of our clinical practice derives from the solidity of the literature on which we stand