Update - Kawasaki disease

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ID Workshop, SAPA Conference
CTICC 9 Sept 2014

Children’s Infectious Diseases
Clinical Trial Unit

Tygerberg Children’s Hospital
Tomisaku Kawasaki - 1st description of Kawasaki syndrome (disease)

1\textsuperscript{st} case – 4y boy

1\textsuperscript{st} & only case of Coombs +ve anaemia
Tomisaku Kawasaki’s timeline -

• Saw 1\textsuperscript{st} case - Jan 1961
  – 2\textsuperscript{nd} case 1 year later
  – Suspected a syndrome
    – 1\textsuperscript{st} 7 cases reported as “non-scarlet fever with desquamation” at a meeting in 1962
    – 50 cases reported in 1967
    – Published in an Allergy Journal
      • “New syndrome” disputed by colleagues
  • Self-limiting and benign or serious?
  • Infantile polyarteritis nodosa = KD?
  • 1970 – 1\textsuperscript{st} nationwide KD survey
    – 10 autopsy cases of sudden death after KD
  • 1\textsuperscript{st} English language publication - 1974
Dr Takajiro Yamamoto

Independently collected cases from 1950’s

1968 – patient with KD developed gallop

Yamamoto T, Kimura J.
Acute febrile mucocutaneous lymph node syndrome (Kawasaki): subtype of mucocutaneous ocular syndrome of erythema multiforme complicated with carditis

Shonika Rinsho (Jpn J Pediatr).

1963 – visiting professor at Cornell, USA – shown a case at Prof. Eichenwald’s grand rounds
In retrospect, 1st cases documented in 1950’s

1st identification outside Japan: Hawaii - 1970’s

Asian children similar clinical picture
KD identified KD from photographs from Japan

Dr. Marian Melish

Dr. Raquel Hicks
Vd Merwe PL, Gie RP et al
Mucocutaneous lymph node syndrome (Kawasaki disease). A report of 2 cases
S Afr Med J 1980; 581014-6

• Pt 1: ECG inferior myocardial infarction
• Pt 2: aneurysm left coronary artery at postmortem
Epidemiology

• **US**
  – Epidemics late winter and spring with 3-year intervals
  – Children from the middle and upper-middle classes
  – ~ 3000 children hospitalized annually
  – More common in Japanese-American

• **Japan**
  – 5000-6000 per year
  – Epidemics 1979, 1982, and 1985

• **Sex:** male-to-female 1.5:1

• **Genetic:** Japan 10x increase risk if affected sibling, 2x increase if parent,
  – similar in US (unpublished)
Cases collected 1970-2012

Burns JC et al. Seasonality of KD. PLOS One 2013; 8: e75429
Cases in top 4 countries

# cases

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>2800000</td>
</tr>
<tr>
<td>Canada</td>
<td>100000</td>
</tr>
<tr>
<td>China</td>
<td>100000</td>
</tr>
<tr>
<td>USA</td>
<td>100000</td>
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Jane C Burns
Incidence per 100,000 <5y of age
Northern Hemisphere – transmissible agent in winter.
Age

- **USA** – 80-90% of admissions < 5 years, median age 3.14 years (1mo-21yrs), 10% under 6 months
- Japanese – Incidence boys 0-4 years old 240 per 100 000 (2007-2008) peak in children 6-11 months
- Also < 6 months or > 5 years
Infant <2 weeks of age

Echo: coronary artery aneurysm day 5

IVIG - rapid improvement
KD = leading cause acquired heart disease in the USA ≤ 5y

ECHO

- asymptomatic coronary artery ectasis
- aneurysm incl giant coronary artery aneurysms with thrombosis

Coronary aneurysms in 25% untreated patients
Mortality

• Japanese registry of 6576 patients - increased mortality in 1st 2 months
• During improvement or recovery phase
• Postmortem - thrombotic occlusion of coronary artery aneurysms & myocardial infarction
Coronary artery lesions

Dilatation

• Internal diameter
  – <5y >3mm
  – >5y >4mm

Persistence abnormalities

Percentage

Months post acute disease

<1  1  2  >12
Morbidity

- Giant CA >8mm greatest risk for myocardial infarction

- Left ventricular function in ~ 50%

- Despite healing in smaller CA, vascular reactivity doesn’t return to baseline: follow up indefinitely

- Arthritis may persist

CA = coronary aneurysm
Risk of aneurysm

- Predicted by the severity of the disease
- Increased fever > 16 days
- Recurrence of fever after afebrile ≥ 48 hours
- Males, < 1 year
- Cardiomegaly
- Laboratory values
  - Low hematocrit
  - Thrombocytopenia
  - Elevated neutrophil/band counts
Thrombocytopenia: a risk factor for acute MI - acute phase KD

- 10 patients
- Coronary aneurysms & acute MI
- Platelet count: 4-12 x 10^4/mm3
- low ESR with high CRP in 7
### Kawasaki Disease - Dx

**Fever >5 days with no other explanation & ≥4 of the 5 following criteria:**

<table>
<thead>
<tr>
<th>Criteria</th>
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<td>Bilateral bulbar conjunctival injection</td>
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<td>Peripheral extremity changes: erythema palms or soles, edema of hands &amp; feet (acute phase) &amp; periungual desquamation (convalescent stage)</td>
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<tr>
<td>Polymorphous rash</td>
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<tr>
<td>Cervical lymphadenopathy (at least one LN &gt;1.5cm in diameter)</td>
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>5 of 6 with no other explanation

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<td>Fever</td>
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American Heart Association 2004
Incomplete KD <5/6 criteria

supplementary lab criteria

Fever of >5 d associated with 2 or 3 clinical criteria, C-reactive protein ≥3.0 mg/dL and/or erythrocyte sedimentation rate ≥40 mm/h with the following criteria:

1. albumin ≤ 3.0 g/dL
2. anemia for age
3. elevation of alanine aminotransferase
4. platelets after 7 d ≥ 450,000/mm³
5. white blood cell count ≥15,000/mm³
6. urine ≥10 white blood cells/high-power field
## Atypical vs Typical

<table>
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<tr>
<th>Features of Typical KD</th>
<th>Features of Atypical KD</th>
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<tr>
<td>Cervical LAD 60%</td>
<td>Cervical LAD 10%</td>
</tr>
<tr>
<td>Rash 90%</td>
<td>Rash 10%</td>
</tr>
<tr>
<td>Peripheral extremity changes 85%</td>
<td>Peripheral extremity changes 60%</td>
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<tr>
<td>&gt;90% mucous membrane changes</td>
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LAD = lymphadenopathy
Tygerberg Children’s Hospital (TCH) Racial breakdown

Race Distribution 2006-2009 TBH

- Mixed: 80.0%
- African: 15.0%
- Asian: 5.0%

N = 21

2006-2009
Longer fever in younger patients (days)
What causes KD?

• Unusual response to infectious agent?
• Seasonality & age
  – Novel retrovirus
  – EBV
  – Parvovirus
  – Coronavirus
• Staphyloccocal toxin mediated?

Autoimmune rather than infectious agent?
Immune dysregulation

- DNA microarrays – upregulation neutrophil response genes (adrenomedullin, grancalcin and granulin)
- Evolving disease - upregulation of CD8 and NK responses & decreased neutrophil response
- Oligoclonal IgA in respiratory tract arteries: respiratory agent?
Polymorphisms with KD

- Inositol 1,4,5- triphosphate 3-kinase
  - Negative regulator of T cell activation
- Angiopoetin up-regulation & vascular endothelial growth factor down-regulation
  - disrupting vascular homeostasis
- Adenosine triphosphate binding cassette
  - Cellular efflux of prostaglandins
- CCR5 gene
  - Chemokine receptor
Hematological & cytokine & immunological events

• Persistent monocytosis post IVIG – coronary artery lesions
• Eosinophilia
• Upregulation apoptosis genes
Animal models

- Intraperitoneal extract of *Lactobacillus casei*
- Coronary disease
- IVIG-responsive

Circulation 2012; 125: 1480
The Dr. who drank infectious broth, gave himself an ulcer, & solved a medical mystery

http://discovermagazine.com/2010

J Robin Warren & Barry J Marshall
Noble prize - 2005
Clinical syndrome

Can be sequential
Always ask for features on history
Dr. N. Cader & Dr. A.R. Badroodien

Pediatric Emerg.

Casuality T1

Dr. Chelsea Jansen

Due to the patient's recent fever and symptoms, an urgent doctor's appointment is scheduled.

Patient was last seen 2 weeks ago for routine check-up. The patient was asymptomatic at that time.

Yesterday, 10/05/2006, patient presented with fever 39.6°C T/C. E/F/T - urgent red cells

Viraemia? Untreated UTI?

Preventive Craig

# of of Viraemia Origin

# of Viraemia

# of other pathology eg. UTI

Preventive Craig

Advisable Winstedt

Preventive Craig
Clinical Course

- Prodrome - respiratory or gastrointestinal illness
- Abrupt onset fever
- Usually receive abx - no response
- Irritable +++
Hands

- Warm inflammatory oedema
- Periungual desquamation
Painful cracked lips
Desquamation

Perineal Urethritis

Cervical
Strawberry tongue
22 months of age

- Fever for 5 days
- Red eyes
- Lt cervical lymph node enlarged
BCG scar reactivation
Unusual features

- Hepatitis
- Hydrops gall bladder
- Meningism
- Interstitial pneumonitis
- Urethritis
- Diarrhoea
- Arthritis
Phases

• **Acute febrile** (days 1-11)
  – myocarditis and pericarditis

• **Subacute** (days 11-21) **sudden death**
  – Persistent irritability, anorexia, conjunctival injection
  – Fever usually resolves by this stage
    • If persists, greater risk of cardiac complications
  – Thrombocytosis 1 million range
  – Desquamation of the fingertips and toes
  – Aneurysms

• **Convalescence** (days 21-60) - labs normalize
Differential diagnosis
Differential
Differential

- Drug reaction
  - incl Stevens-Johnson syndrome
- Strep pharyngitis & Scarlet fever
- Toxic shock syndrome
- Measles
- Adenovirus
- Periodic syndrome
- Polyarteritis nodosa
- Hg poisoning
Treatment - effective

- IVIG 2g/kg IVI 12hrs
- Aspirin
  - 80 - 100mg/kg’day - 4 doses X 2w
  - 3 to 5mg/kg 6-8w or longer if coronary arteries
Treatment

- Terai et al (1997), prevalence of CA assessed by blinded echo at 30 days and >60 days
  - Aspirin alone: CA 26% (30 days) 18% (>60 days)
  - IVIG 2mg/kg and aspirin: CA 4% (30 days) and 4% (>60 days)

- Oates-Whitehead 2003 Meta-analysis
  - RR of IVIG + aspirin versus aspirin 0.35 95% CI 0.15-0.83
  - 2g much better than 400mg
Timing of Treatment

- IVIG most effective early
- <5 days = 5 – 9 days
- <5 days - relapse?
- Expert consensus – treat within 4 days
- After day 10 – still treat if any inflammation
IS THERE A ROLE FOR CORTICOSTEROIDS IN KAWASAKI DISEASE?

“The arrival of a good clown exercises more beneficial influence upon the health of a town than twenty asses laden with drugs.” —Thomas Sydenham (1624-1689)

issue of The Journal, evaluates corticosteroids as an adjunct to IVIG and salicylates for primary therapy of KD.⁸

In reviewing the published experience with corticosteroids in KD, it is important to distinguish between its use as primary therapy and as “rescue therapy” for KD. Most previous
No response / Relapse

- IVIG resistance: 9 – 34%
- T >38°C post 48 hours
- ↑ risk CA abnormalities

Modalities
- Pulsed steroids
- TNFα blockade
- Immunosupression
  - Cyclophosphamide
  - Cyclosporin A
Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial

Adriana H Tremoulet, Sonia Jain, Preeti Jaggi, Susan Jimenez-Fernandez, Joan M Pancheri, Xiaoying Sun, John T Kanegaye, John P Kovalchin, Beth F Printz, Octavio Ramilo, Jane C Burns
TNF inhibition in acute Rx
No benefit

- 196 children KD
  - 1 dose infliximab 5mg/kg plus standard therapy
  - Placebo plus standard therapy

- No difference in treatment resistance (temp >38°C: 36 hours to 7 days post IVIG), both groups 11%

- No effect on CA development
Experimental

- Ulinastatin- urinary trypsin inhibitor with anti-inflammatory properties (neutrophil targeted)
  - Not effective as monotherapy
KD shock

- In acute phase
- Hypotension & shock
- LV systolic dysfunction
- Mitral regurgitation
- CA
- Resistant to Rx
Predicting IVIG non-responsiveness

Kobayashi T Circulation 2006; 113: 2606
IVIG (+ aspirin) ± prednisolone in severe KD: randomised, open-label, blinded-endpoints trial

- IVIG 2g/kg + Aspirin (30mg/kg/day)
  - N = 125
- + Methylprednisolone 2mg/kg/day X15 days post normal CRP
  - N = 123
- Risk score ≥5
- Fever ≤9 days
- No CA abnormalities pre enrolment

Raise study: Kobayashi et al Lancet 2012; 379: 1613
CA abnormalities lower in IVIG + pred than IVIG alone

Risk difference 0·20, 95% CI 0·12–0·28, p<0·0001)
Infliximab Plus Plasma Exchange Rescue Therapy in Kawasaki Disease

Kaori Sonoda, MD¹, Masaaki Mori, MD², Tatsunori Hokosaki, MD¹, and Shumpei Yokota, MD¹

Objective To evaluate infliximab (IFX) in patients with Kawasaki disease (KD) that was unresponsive to additional intravenous immunoglobulin (IVIG) therapy and subsequent rescue with supplementary plasma exchange (PE) in patients unresponsive to treatment.

Study design We studied 76 patients with KD who received IVIG therapy twice and were unresponsive to additional IVIG.

Results Seventy were treated with IFX alone (92.1%). Six patients who were unresponsive IFX (7.9%) were further treated by PE. This resulted in disappearance of fever and other clinical symptoms, and improvement of laboratory data. There was no severe life-threatening adverse events. Twelve of the 76 cases had developed coronary artery dilatation, and 3 had coronary artery aneurysm within 1 month of disease onset. At the end of follow-up, in all cases, coronary artery lesions were suppressed or reversed.

Conclusions Treatment of intractable KD with sequential IVIG, IFX, and PE treatments in a step-wise protocol was effective. (J Pediatr 2014;164:1128-32).
Long term issues

• Continued inflammation in CA’s
• Role for statins?
KS in adults

- 57 cases 18 – 30 years of age
- 2 cases & literature review
- Seve et al Sem Arthritis Rheumatol 2005: 34: 785-92
KS & HIV

REVIEW

Kawasaki-like syndromes in HIV-infected adults

K. Stankovic a,*, P. Mialhes b, D. Bessis c, T. Ferry d, C. Broussolle a, P. Sève a

J Infection 2007; 55: 48
Adult KD

- 20 cases
- High viral loads
- Low CD4
- Hepatitis virus co-infection
Acknowledgements

• Helena Rabie - TCH
• Lisa Frigati – TCH
• Kate Carkeek - TCH