Kawasaki Disease

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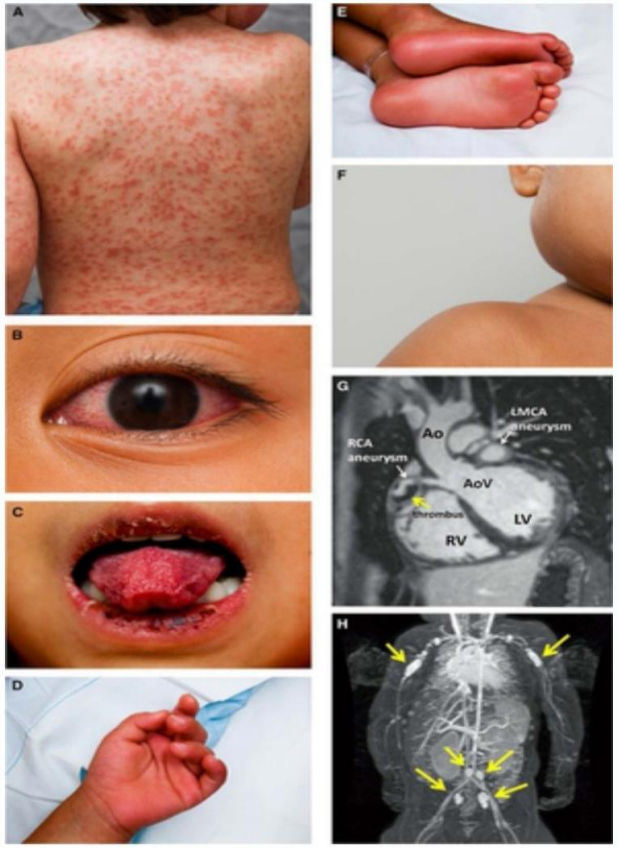
Introduction

- Rare systemic inflammatory disease
- First described in 1967 report by Japanese pediatrician Tomisaku Kawasaki
- Mostly children less than 5 years of age
- The most feared complication of KD :

  coronary artery abnormality development
- Pathogenesis of KD : unknown



Epidemiology

- Varies greatly by geographic location and seasonality
- The highest rates seen among Asian/Pacific Islanders
- Mostly children < 5 years of age, with a male predominance
- The lowest recorded rate among white children

- Japanese KD nationwide survey reported an increased rate over time from 218.6 per 100,000 in 2008 to 243.1 and 330.2 in 2011 and 2015 respectively

Pathogenesis

- Genetics
- Vaccine Exposure Theory
- Infectious Theory/Seasonality
- Immune Factors/Dysregulation

Genetics

- Predilection for children of East Asian and Pacific Islander descent, even with transmigration
- Concordance risk in identical twins at ~ 13%
- Increased incidence of KD in children whose parents have a history of KD
- Higher occurrence of KD in siblings of affected patients

Genetics

- KD **does not** appear to follow Mendelian pattern of inheritance
- Several SNPs in different genes and gene regions :**caspase 3 (CASP3), inositol 1,4,5-trisphosphate kinase-C (ITPKC), CD40, FCGR2a, and B-cell lymphoid kinase** (BLK)
- Many of the SNPs associated with KD have been identified in other inflammatory diseases such as RA, UC, SLE, and systemic sclerosis

Vaccine Exposure Theory

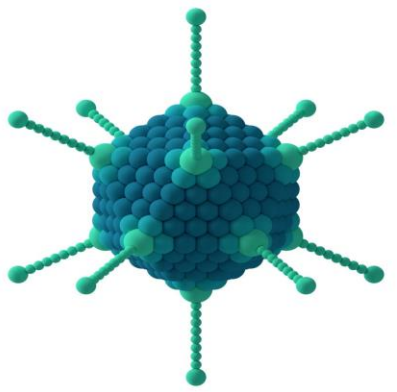
- There is currently no evidence to suggest that vaccine administration is associated with development of KD

Infectious Theory/Seasonality

- The leading theory for the pathogenesis of KD
- Peak in January and spring to summer (March–June)
- Tropospheric wind patterns in different locations
- Significant overlap of clinical features between KD and other infectious agents, most notably Scarlet fever, the newly described multisystem inflammatory syndrome and adenovirus

Infectious Theory/Seasonality

- Positive low titer adenovirus infection in 10% of patients
- Peak incidence in late infancy (9–11 months)
- Higher occurrence of KD cases among siblings either on the same day or within 10 days of the initial presentation



Immune Factors/ Dysregulation

- No infectious causes have been identified as potential underlying etiologies
- So yet the theory is an unknown stimulus triggers an inflammatory cascade
- The innate immune system may be activated via detection of either pathogen-associated molecular patterns , or damage-associated molecular patterns.
- Different kinds of cytokines play role in KD, and some of well studied ones are: IL-1, IL-18, IL-6, TNF-a, IFN-gamma, and IL-8 Interleukin-1 has direct inflammatory effects on coronary artery endothelial cells.

Immune Factors/ Dysregulation

- The adaptive immune system:
- We have increased pro inflammatory and regulatory T cells in the acute phase of KD
- Studies have shown we have IgA producing plasma cells in tissues and walls of coronary arteries
- Several auto antibodies against myocardial , endothelial proteins have been detected

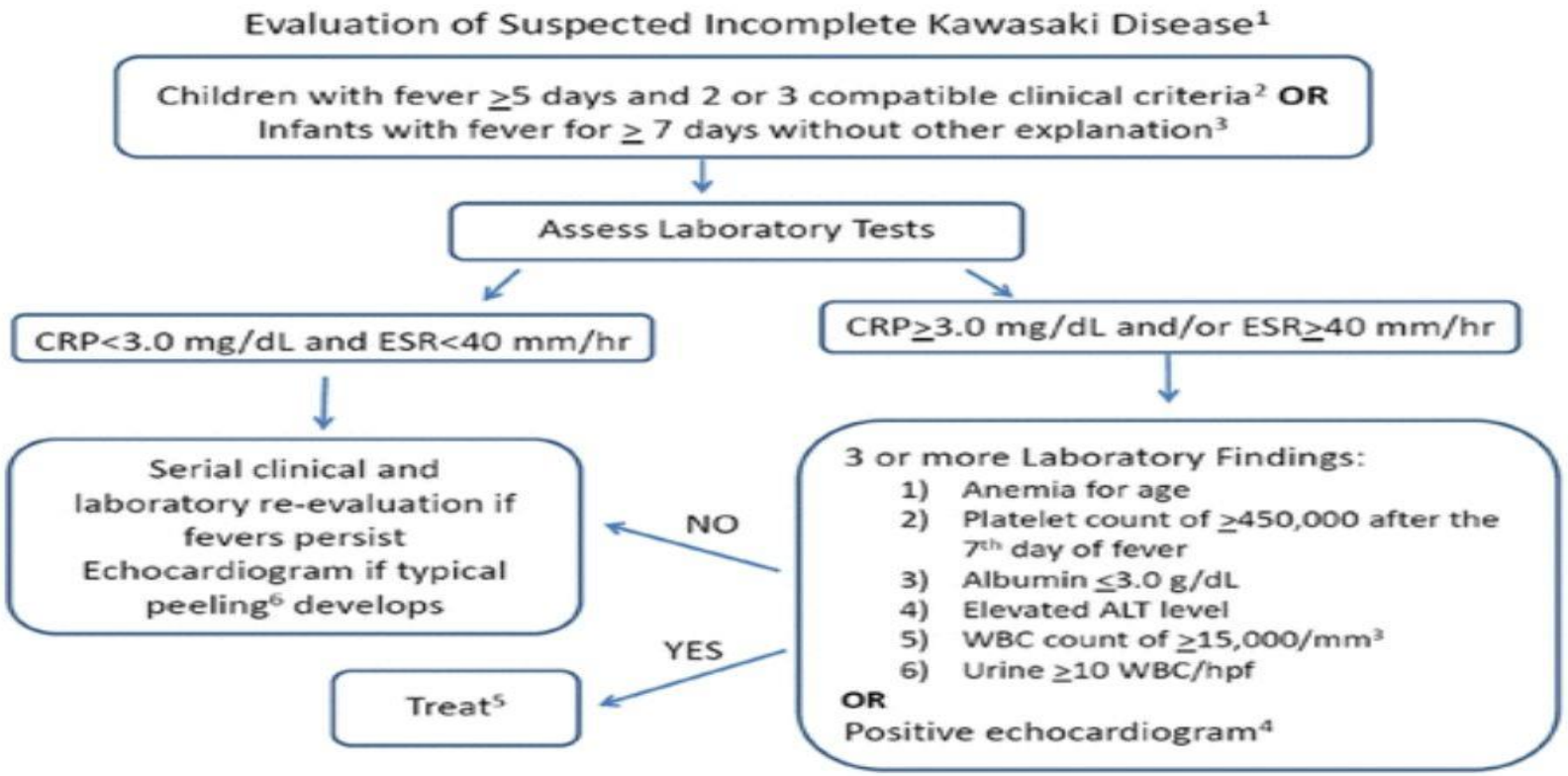
Immune Factors/ Dysregulation

- Following administration of IVIG, we see an expansion of regulatory T cell populations and normalization of B cell activating factor
- This is associated with subsequent clinical improvement during the acute phase of KD
- Based on the evidences mentioned above, adaptive immune system plays an important role in the KD, specially the cardiac symptoms

Diagnosis

- There is no diagnostic test for KD and the diagnosis is based on clinical criteria and excluding other similar clinical entities
- Patients with classic (complete) KD are easier to diagnose and patients who do not fulfil all criteria are referred as incomplete KD who are also at risk of coronary disease, so :
- Any child with prolonged unexplained fever with any of the principal clinical features should be further evaluated for KD with consideration of echocardiography.

The American Heart Associated (AHA) created an algorithm to aid in evaluation of suspected KD patients who do not meet the diagnostic criteria



Diagnosis

- KD mostly have 3 phases: acute , sub acute and convalescent phase
- Acute :
- High-spiking fevers (typically > 39.0 °C)
- Mucosal changes
- Conjunctivitis
- Polymorphous rash
- Lymphadenopathy
- The acute febrile
- Phase lasts anywhere from 7 to 14 days

Diagnosis

- Sub acute:
- Is often an asymptomatic period after the febrile episode subsides and extends approximately 4 weeks
- May still have desquamation of the digits , arthralgia , and abnormal lab findings
- This period has the greatest risk of developing cardiac diseases , namely coronary artery aneurysms

Diagnosis

- Convalescent phase:
- Typically an asymptomatic period
- 4–8 weeks after onset of initial illness
- There is still risk of cardiac aneurysms (significantly decreased)

Laboratory Analysis and Workup

- Kawasaki disease is a *clinical diagnosis* based on set diagnostic criteria. Laboratory findings, although nonspecific, *are useful in supporting a diagnosis of KD*, particularly when the clinical manifestations are non-classic.

Table 3 Common laboratory findings in KD

White blood count (WBC)	> 15,000 per mm^3 (neutrophillia with immature forms)
Hemoglobin	Anemia (for age)
Platelets	> 450,000 per mm^3 (peaks in the third week)
Sedimentation rate	> 40 mm/h
CRP	> 3.0 g/dL
Albumin	< 3.0 g/dL
Ferritin	Elevation above normal range
Alanine aminotransferase (ALT)	Elevation above normal range
GGT	Elevation above normal range
Urine WBCs	> 10 WBCs per high powered field
Cerebrospinal fluid	Mononuclear pleocytosis without hypoglycorrhachia and/or elevated protein

- The use of platelet-activating factor (PAF) and its acetyl-hydrolase (PAF-AH) in predicting KD

Diagnostics/Imaging

- The most feared sequelae of KD is development of coronary artery abnormalities. *Echocardiography* remains the standard imaging modality to evaluate for both coronary artery dimension as well as other cardiac abnormalities.
- Using of coronary artery sizes according to age.
- Utilizing of Z scores when classifying CALs

Diagnostics/Imaging

- Echocardiography surveillance is typically performed at diagnosis, 1–2 weeks after diagnosis, and then again 6– 8 weeks later (assuming no complications).
- Factors associated with increased risk of developing CALs: male sex, age < 12 months or > 8 years, fever duration > 10 days, leukocytosis > 15,000 per mm3 , low hemoglobin (< 10 g/dL), thrombocytopenia, hypoalbuminemia, Hyponatremia, and persistent fever or recurrence of fever > 36 h after IVIG administration
- Other imaging modalities utilized: magnetic resonance angiography, computed tomographic angiography, and cardiac catheterization if warranted.

Differential Diagnosis

- Clinical manifestations that do not align with the diagnostic criteria for KD should prompt investigation of other causes
- Be noted Concurrent infection with another pathogen
- ***Multisystem inflammatory syndrome in children (MIS-C)***

Table 4 Differential diagnosis of Kawasaki disease

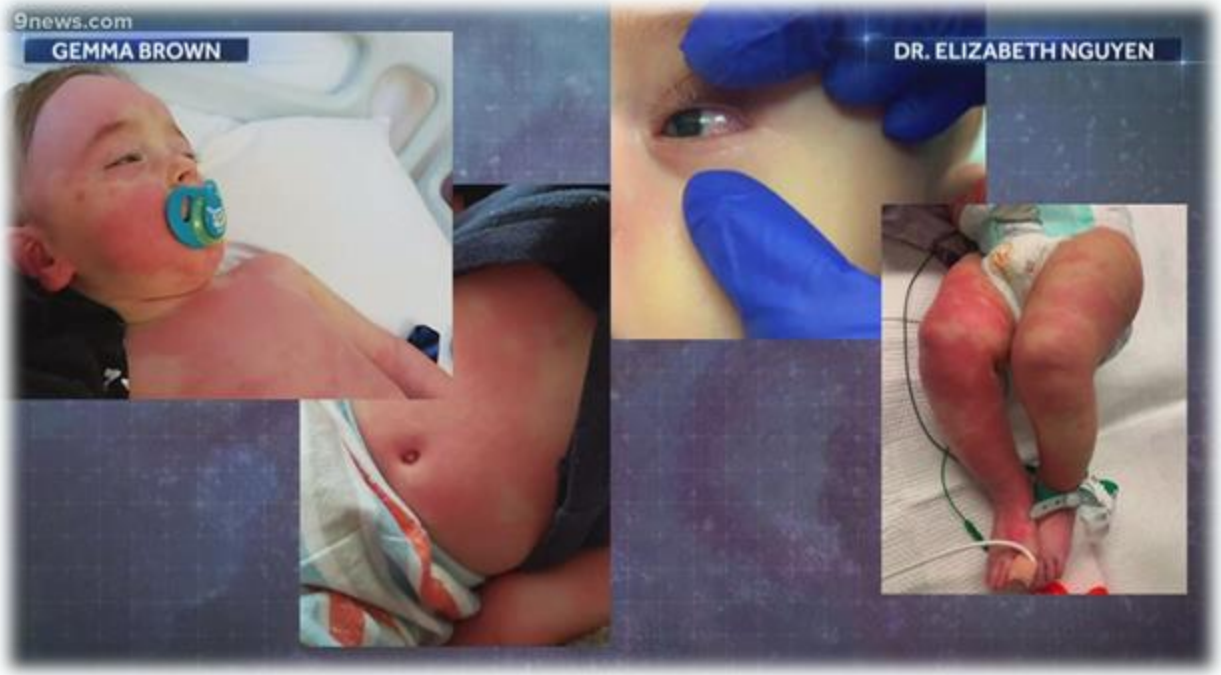
Viral	Measles Adenovirus Enterovirus Epstein-Barr virus
Bacterial	Scarlet fever Acute rheumatic fever Rocky mountain spotted fever Leptospirosis Cervical lymphadenitis
Toxin-mediated	Staphylococcal scalded skin syndrome Toxic shock syndrome
Hypersensitivity reactions	Drug hypersensitivity reaction Steven-Johnson syndrome
Rheumatic disease	Juvenile idiopathic arthritis Polyarteritis nodosa Reactive arthritis
Toxicity	Acrodynia (mercury poisoning)
Other	Multisystem inflammatory syndrome in children

MIS-C

- April 2020 in the UK
- Inflammatory condition + association with COVID-19
- Persistent fever, conjunctivitis, mucositis, lymphadenopathy, rash, evidence of multisystem organ involvement, and elevated inflammatory markers
- Respiratory symptoms and abdominal pain
- CDC : individuals less than 21 years of age presenting with fever (> 38.0 °C), laboratory evidence of inflammation, and clinically severe illness requiring hospitalization with multisystem organ involvement. Patients must have evidence of exposure to COVID-19 within 4 weeks prior to onset of symptoms
- Exclude plausible alternative diagnoses

differences compared to KD

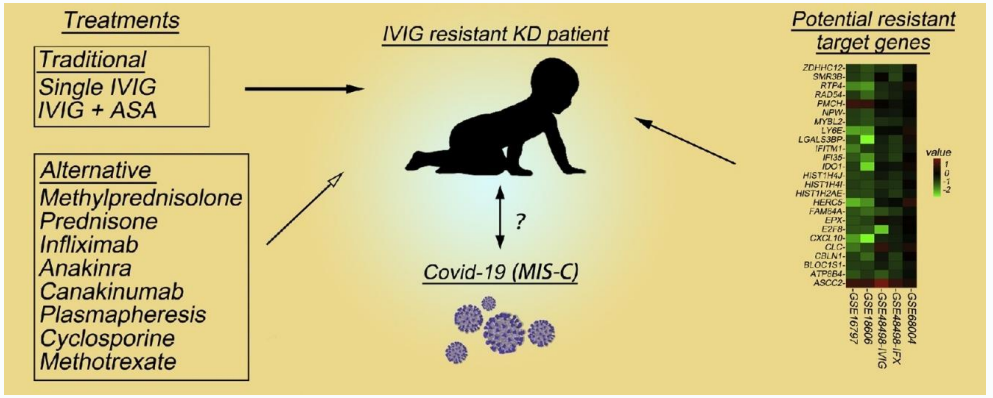
- MIS-C typically presents after the age of 5
- There appears to be a higher incidence in children of Afro-Caribbean descent



Primary Treatment

- Intravenous Immunoglobulin (IVIG)
- ASA

IVIG



- IVIG is most effective when administered within 10 days of onset of fever
- Decreases the risk of coronary artery aneurysm formation from 20–25% to 3–5%
- Single infusion of ***high-dose IVIG at 2 g/kg*** together with ***acetylsalicylic acid*** (ASA)
- IVIG-resistant … second dose of IVIG to help prevent sequelae

Additional considerations regarding IVIG therapy

- Active vaccinations, i.e., measles and varicella vaccinations are contraindicated for 11 months after administration of IVIG and known physiologic ESR elevations after IVIG preclude its use to assess response to therapy

ASA

- Moderate-dose (30–50 mg/kg/day) or high-dose (80 to 100 mg/kg/day)
- Difference between low-dose (3-5 mg/kg/day) ASA versus high-dose ASA
- Acute phase → Every 6 h…continue high-dose ASA until the 14th day of illness
- After the acute phase → 3–5 mg/kg (low-dose)
- Convalescent phase → low-dose ASA

continue or discontinue therapy ?

- Around 6 – 8 weeks pending any CALs (coronary artery lesions) on echocardiogram
- Patients who are at high risk of treatment resistance
- with coronary sequelae
- → adjunctive treatments

Adjuvant Therapy and Treatment Options for Cases Refractory to IVIG and ASA:

- Corticosteroids
- Tumor Necrosis Factor (TNF) Inhibition
- Interleukin 1 Inhibition
- Calcineurin Inhibition
- Other Therapies

Corticosteroids

- Strong anti-inflammatory properties-and overall improved outcomes
- In patients at particularly high risk for development of CALs may benefit
- A 2016 meta-analysis of 16 studies by Chen et al
- A 2017 Cochrane review
- Early use of corticosteroids during the acute phase appears to be more beneficial than in refractory (IVIG-resistant) cases.

Tumor Necrosis Factor (TNF) Inhibition

- TNF and IL-1 beta have both been implicated in the vascular endothelial cell damage and CALs seen in acute KD
- Infliximab, whose use may decrease the duration of fever and the length of hospitalization as well as aid in normalization of acute phase reactants.

A recent trial with Etanercept for acute phase KD

- Interleukin 1 Inhibition

- Calcineurin Inhibition

Other Therapies

- Plasma exchange – Cyclophosphamide –Methotrexate, and even Rituximab

- IL-6 inhibitors are not currently used in refractory cases of KD (Tocilizumab)

Primary Prevention of Thrombosis

- Patients with no evidence of CALs
- Patients with small CALs
- Patients with moderate-sized aneurysms
- Children with persistent large or giant aneurysms (internal luminal diameter ≥8mm)
- Role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (Statins) in children with KD and CALs.

Prognosis and Long-Term Management

- The case-fatality rate in the United States and Japan is less than 0.2%.
- The AHA 2017 guidelines for diagnosis, treatment, and management of KD provide a detailed risk classification scheme that can be utilized for follow-up guidance.


THANKS
for your
ATTENTION