Kawasaki Disease

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CC : تب و راش

PI : آ.م ، کودک ۵/۴ ساله ای است که با شکایت راش جلدی ماکولوپاپولر جنرالیزه وتب طول کشیده (بیشتر از۵روز) که به درمان تک دوز پنادر و استامینوفن پاسخ نداده است ، در تاریخ ۱۴/۷ به بیمارستان مرکز طبی اطفال آورده شده است و جهت بررسی از نظر کاوازاکی در بخش عفونی بستری شده است

PMH : حاصل NVD است .وزن هنگام تولد ۶۰۰/۳ کیلو گرم بوده است.آپگار مناسب داشته و سابقه زردی خفیف فیزیولوژیک را عنوان می کنند. واکسیناسیون کامل است و سابقه ابتلا به بیماری خاصی را ندارد.

FH : پدر و مادر غیر منسوب و نکته خاصی وجود ندارد

DH : پنادر و قطره استامینوفن

VS: BP : 100/70 T : 39^{oc} PR : 90 RR : 25

PhE :

H & N

Sclera : not icteric

No lymphadenopathy

CHEST

Heart : NL

Lung : NL

ABDOMAN

No tenderness

No organomegaly

EXTREMITIES

Edematous

No cyanosis

No clubbing

BUT

generalized maculopapular rash
on the trunk , hands, and feet

Impression : R/O of Kawasaki disease (KD)

Condition : ill but not toxic

Position : out of bed ?????????

Nutrition : PO, regular regimen

۱۴/۷/۸۶

CBC , diff, Plt
ESR, CRP
U/A , U/C
BUN, Cr
ALT, AST
Alb , total pr.
Na, K
Abdomen sonography
Echocardiography
Tab Acetaminophen 500 mg ½ tab PRN *

۱۵/۷/۸۶

CBC

RBC :5000
Hgb :11mg/dl
Hct :34%
MCV :82mm^3
MCH :29pg/cell
MCHC :32g/dl
Plt : 400000

WBC : 15400
Neut : 69%
Lymph :27%
Mono :3%
Eos :1%

Na : 141
K : 4

U/A

WBC : 11
No bacteria
No pr., sugar, blood

ESR : 110 mm
CRP : ++++

Diagnosis of

Kawasaki Disease

is made

۱۵/۷/۸۶

بیمار همچنان تب دار است.($39.5\ ^{o}C$)

پیگیری آزمایشات بیمار

1) Tab Aspirin 500 mg QID
2) IVIG 40 g infusion over 12 hrs

1) Tab Acetaminophen ⟶ DC

2) Cap Omeprazole 20 mg once daily

۱۶/۷/۸۶

بیمار همچنان تب دار است.

U/C : -
ALT : 22 U/ml
AST : 18 U/ml
Alb : 3.5 g/dl
Total pr : 6.8 g/dl
BUN :13 mg/dl
Cr : 0.7 mg/dl
Echo : NL
Sono : NL

تب بیمار قطع شده است.

بیمار با دستور دارویی زیر مرخص است :

Tab Aspirin 500mg QID for 4 more days then
100 mg daily for 2 months

Echocardiography 2 weeks later

Kawasaki Disease

History

- **First described in Japan in 1967 by Tomisaku Kawasaki**
- **Acute febrile multisystem vasculitic syndrome**
- **Unknown etiology**
- **Predominantly affects infants and young children**

Kawasaki disease (KD, also called mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood.

- It is typically a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy.

- However, complications such as coronary artery aneurysms, depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and lead to significant morbidity and mortality.

- The frequencies of aneurysm development and mortality have been dramatically decreased as a result of intravenous immune globulin (IVIG) therapy.

- Expeditious diagnosis is critical to achieve the optimal treatment result.

Epidemiology

Gender

-Male to female ratio : 1.5 :1

Race and ethnic background

-More common in individuals of Asian background

- Annual incidence rate in Japan : 100-112/100000
- Incidence rate in white children : 10/100000
- Genetics rather than environmental basis
- No specific HLA marker

Age

-Occurs exclusively in children → 50% younger than 2yrs; 80% younger than 5yrs

- Mortality rate 3× higher in children ≤ 1yr
- Mortality peak is in 15^{th}-45^{th} days of disease onset
- Mortality rate in Japan : 0.08 – 2%

Epidemiology

Recurrent

-At least 3 months after resolution

- Recurrent rate :1.9-3% after ≥ 3 yrs follow up

-More common within the first 2 yrs

- More common in male children

Family cases

-Twins (13%) > non twins (2.1%)

Geography

-More commons in countries with temperate climate, but no significant differences

Seasonality

-Most prevalent in winter-spring, peaks in December and January

Communicability

- Little evidence for person-to-person transmission

Etiology

-Remains unknown

- An infectious cause is strongly suggested

- Immunologic response triggered by microbial agents

- No association between kawasaki and drugs and environmental pollutants

Pathology and Pathogenesis

- Generalized vasculitis most severe in the medium-sized arteries, with marked predilection for coronary arteries

CLINICAL MANIFESTATIONS

- KD is characterized by systemic inflammation manifested by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, rash, extremity changes and lymphadenopathy.

- These clinical signs are the basis for the diagnostic criteria for KD (table 1).

Diagnostic criteria for Kawasaki disease

The diagnosis of Kawasaki disease requires the presence of fever lasting at least five days without any other explanation combined with at least four of the five following criteria:
Bilateral bulbar conjunctival injection
Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase)
Polymorphous rash
Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter)

CLINICAL MANIFESTATIONS…

- These findings are often not present at the same time.
- As an example, the only clinical features some patients have developed by the time of admission are fever and cervical lymphadenopathy (KD with isolated cervical lymphadenopathy, KDiL).
- In one case series, these patients tended to be older and have a more severe course, with increased risk of coronary artery disease and lack of response to intravenous immune globulin.

CLINICAL MANIFESTATIONS…

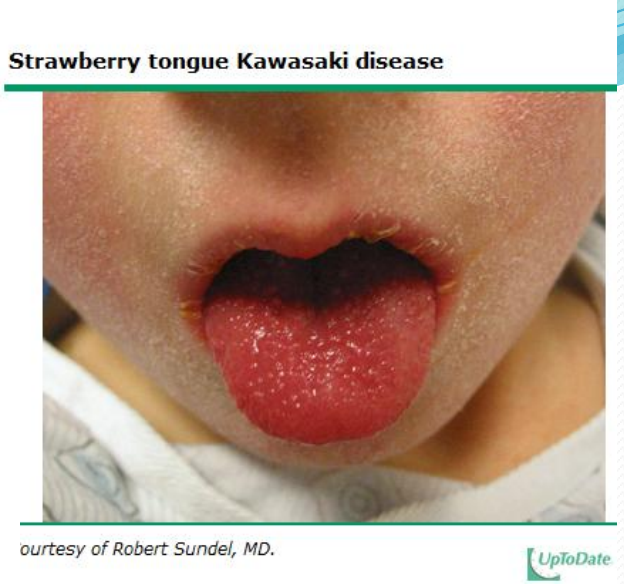
- Fever is the the most consistent manifestation of KD.
- It reflects elevated levels of proinflammatory cytokines such as tumor necrosis factor and interleukin-1, which are thought to mediate the underlying vascular inflammation.
- Fever is minimally responsive to antipyretic agents, and remains above 38.5ºC during most of the illness.
- Patients are often described as irritable.
- *The diagnosis of KD should be considered in all children with prolonged unexplained fever ≥5 days.*

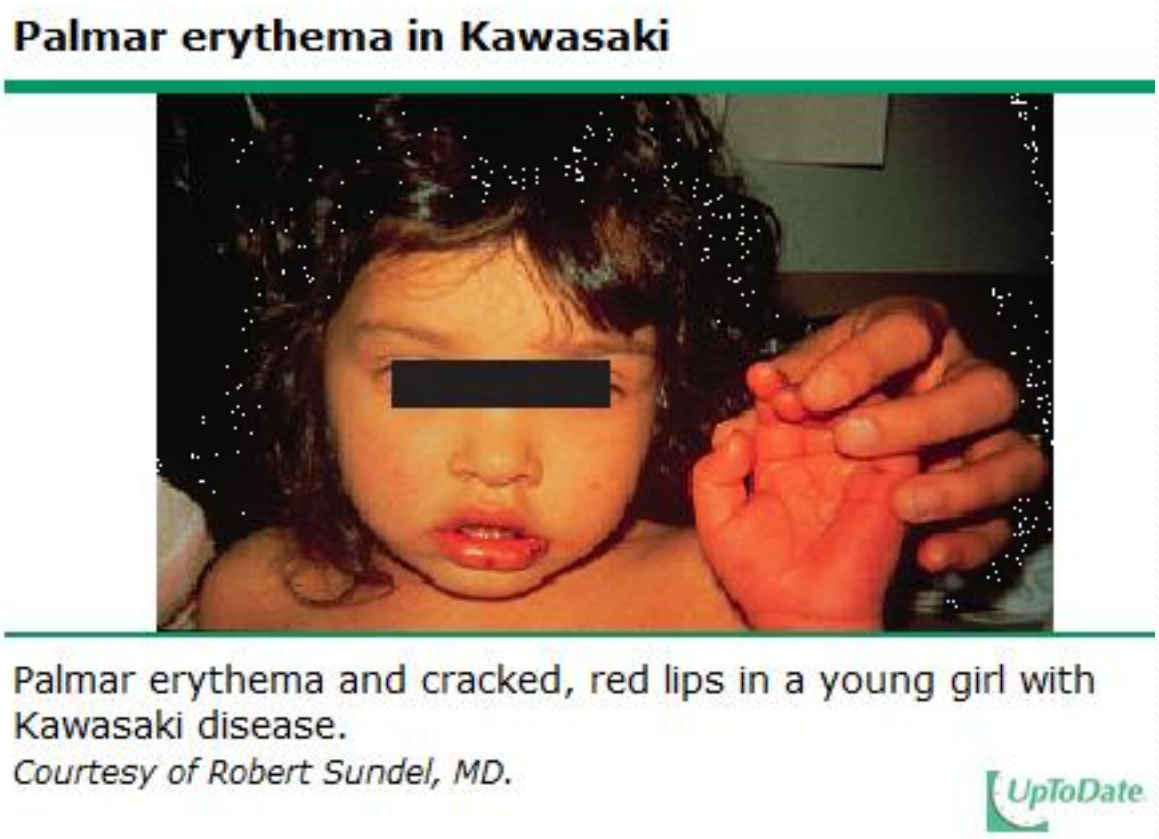
Conjunctivitis

- Bilateral nonexudative is present in more than 90 percent of patients.
- Typically begins within days of the onset of fever
- Children also are frequently photophobic, and anterior uveitis may develop.

Mucositis

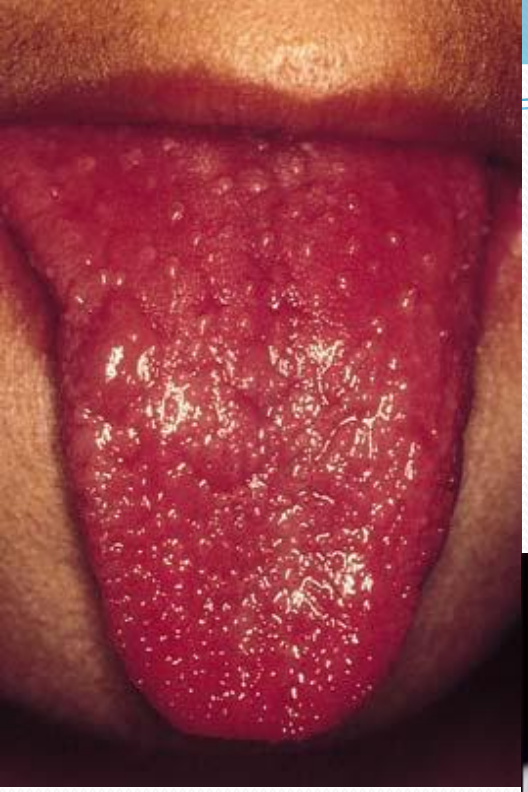
- As KD progresses, mucositis often becomes evident. Cracked, red lips and a strawberry tongue are characteristic

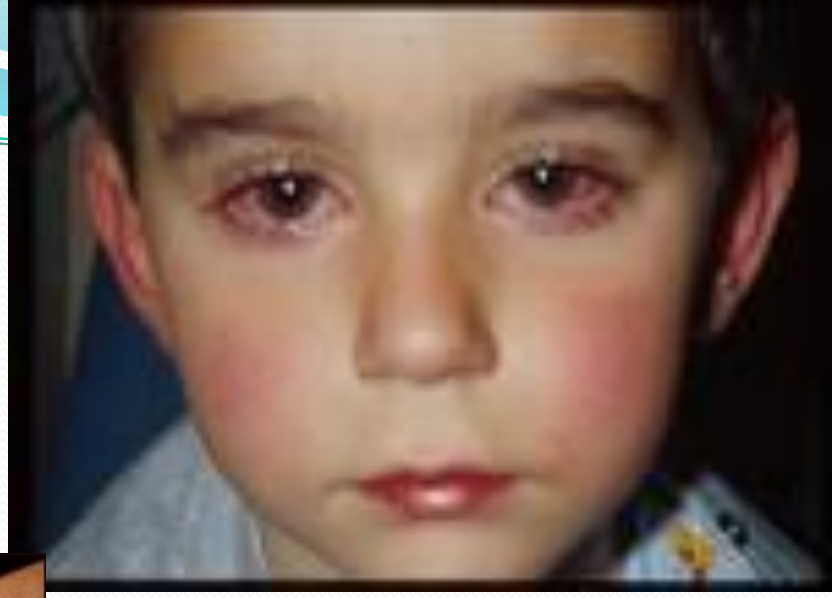




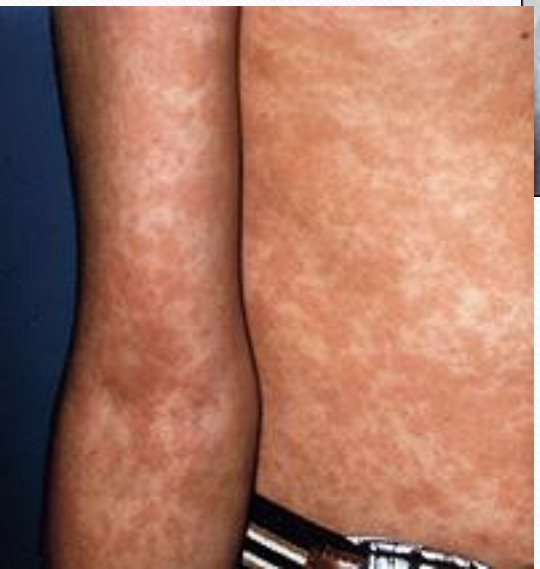
Rash

- The cutaneous manifestations of KD are polymorphous.
- The rash typically begins as erythema and desquamation, followed by macular, morbilliform, or targetoid skin lesions of the trunk and extremities.
- Vesicular or bullous lesions are rare, but KD may trigger a psoriasiform eruption in children not previously recognized to have psoriasis.






A.D.A.M.




A.D.A.M.

Extremity changes

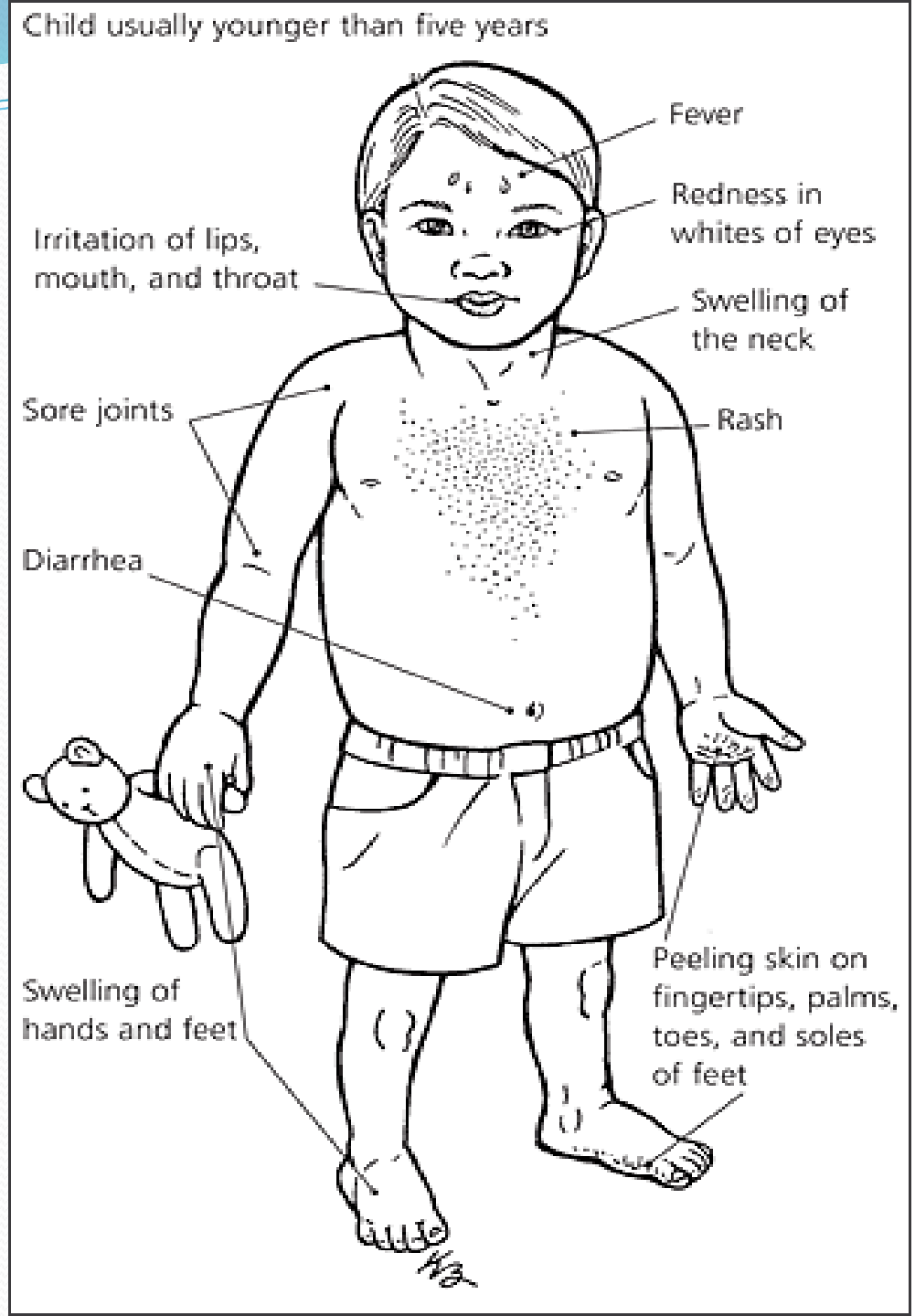
- Changes in the extremities are generally the last manifestation to develop.
- Children demonstrate an indurated edema of the dorsum of their hands and feet, and a diffuse erythema of their palms and soles .
- In addition, arthritis has been reported in 7.5 to 25 percent of patients.
- In the children with arthritis, the large joints (ie, knee, ankle, and hip) were primarily involved.

Cervical lymphadenopathy

- Cervical lymphadenopathy is the least consistent feature of KD, absent in as many as half to three-quarters of children with the disease.
- When present, lymphadenopathy tends to involve primarily the anterior cervical nodes overlying the sternocleidomastoid muscle
- Diffuse lymphadenopathy or other signs of reticuloendothelial involvement (eg, splenomegaly) should prompt a search for alternative diagnoses.

Other findings

- The following nonspecific symptoms and their frequency commonly occur in children within the first 10 days before diagnosis of KD but are not included in the diagnostic criteria.
- Diarrhea, vomiting, or abdominal pain — 61 percent
- Irritability — 50 percent
- Vomiting alone — 44 percent
- Cough or rhinorrhea — 35 percent
- Decreased intake — 37 percent
- Weakness — 19 percent
- Joint pain — 15 percent


Child usually younger than five years
Fever
Redness in whites of eyes
Irritation of lips, mouth, and throat
Swelling of the neck
Sore joints
Rash
Diarrhea
Swelling of hands and feet
Peeling skin on fingertips, palms, toes, and soles of feet
KATHRYN BORN/AAFP

Clinical phases of illness

Acute (8-30 days)

Fever, rash, conjunctival injection, strawberry tongue, edema and erythema of hands and feet, lymphadenopathy, aseptic meningitis, mild hepatic dysfunction, tachycardia, pericardial effusion

Subacute (3-4 wks)

-The physical findings rapidly disappear
- Child may remain irritable
- Decreased activity
- Conjunctional injection may persist
- Arthritis may develop
- Desquamation
- Thrombocytosis

Convalescent (6-8 wks)

- Resolution of sign and symptoms
- Normal ESR

Laboratory features of kawasaki disease
Leukocytosis with neutrophilia
Elevated ESR
Positive CRP
Anemia
Thrombocytosis
Sterile pyuria
Hypoalbuminemia
Elevated serum transaminases
Blood lipid abnormalities

Complications

- Although complications primarily reflect cardiac sequelae including coronary artery aneurysms, other non-cardiac complications also may be seen.

Shock

- KD shock syndrome, defined as sustained systolic hypotension (decrease in blood pressure greater than 20 percent from baseline) or clinical signs of poor perfusion, is a potentially life-threatening complication .

- Patients with shock syndrome were more likely than patients who were hemodynamically stable to have consumptive coagulopathy and cardiac abnormalities including impaired left ventricular systolic function, mitral regurgitation, and coronary artery abnormalities .

- They were also less responsive to initial intravenous immunoglobulin therapy, and more commonly required additional treatment of their KD.

Cardiac complications

- The major complication of KD is coronary artery aneurysms, however other cardiac sequelae occur including decreased myocardial contractility, coronary arteritis without aneurysms, mild valvular regurgitation (primarily mitral valve involvement), and pericardial effusion.

Cardiac complications…

- Coronary artery disease — Some degree of coronary artery involvement appears to be present in all children with KD.
- Coronary artery (CA) aneurysms, occur in 20 to 25 percent of untreated children with KD , but only 4 percent of those who receive adequate therapy.

Several clinical findings at presentation have been associated with an increased risk of developing CA aneurysms:

- Age younger than one year
- Male sex
- Fever ≥14 days
- Serum sodium concentration <135 mEq/L
- Hematocrit <35 percent
- White cell count >12,000/mm3
- Age older than nine years

Cardiac complications…

- The risk of CA aneurysms is increased in children younger than one year and older than six years of age.
- It is not clear whether this increased risk is a result of late diagnosis, which delays administration of IVIG therapy, or an intrinsic susceptibility to coronary artery dilatation in these populations.
- *IVIG treatment administered during the first 10 days of illness reduces the prevalence of CA aneurysms five-fold compared to later administration.*

Cardiac complications…

- The prognosis of CA aneurysms depends on the size and shape of the aneurysm.
- The best prognosis is associated with fusiform aneurysms of <8 mm in diameter.
- In contrast, giant CA aneurysms, with an internal diameter >8 mm, have the highest risk of morbidity and mortality.
- *Up to one-third of such aneurysms become obstructed, leading to myocardial infarction, arrhythmias, or sudden death.*
- *Treatment with IVIG during the first 10 days decreases the incidence of giant aneurysms by more than 95 percent.*

Cardiac complications…

- Depressed myocardial contractility
- Depressed myocardial contractility may be caused by *myocarditis, cardiomyopathy, or left ventricular dysfunction.*
- Depressed myocardial contractility, occasionally progressing to **heart failure**, may occur during the acute illness.
- Normal contractility typically is restored following treatment with IVIG, suggesting that cytokines contribute to the myocardial dysfunction.

Cardiac abnormalities in kawasaki disease

Acute Stage

Pericardial effusion

Decreased myocardial function

Mitral regurgitation

Brightness of coronary artery wall on echo

Enlargement of coronary arteries

Subacute Stage

Coronary aneurysms

Mitral or aortic regurgitation (rare)

Coronary aneurysm rupture (rare)

Convalescent Stage

Persistent coronary aneurysms

Regressed coronary aneurysms (residual fibrosis)

Coronary artery stenosis

Coronary aneurysm rupture

Noncoronary vascular involvement

- Vascular changes also can occur in **peripheral and visceral arteries:**
- Peripheral arterial obstruction can lead to ischemia and gangrene;
- this complication generally accompanies other manifestations of severe disease such as giant coronary artery aneurysms and aneurysms in peripheral arteries.

Associated noncardiac features of Kawasaki Disease

ARF

Arthritis or arthralgia

Aseptic meningitis

Marked irritability

Hydrops of gallbladder

Abdominal pain, diarrhea

Urethritis

Hepatic dysfunction, obstructive jaundice

Preceding respiratory illness

Erythema and induration of BCG vaccine site

Peripheral gangrene

Auditory abnormalities

Facial nerve palsy

Treatment for kawasaki disease

Acute and Subacute Stages

IVIG: 2g/kg inf over 10-12 hrs plus

Aspirin:80-100mg/kg QID until 14th illness day and patient afebrile at least 3 - 4 days, then 3 - 5 mg/kg/d for 6-8wk

Convalescent Stage

No coronary abnormalities : no therapy

Transient coronary abnormalities : aspirin 3-5 mg/kg/d until resolution

Persistent small to medium coronary aneurysms : aspirin 3-5mg/kg/d

Giant or multiple small coronary aneurysms : aspirin 3-5mg/kg/d ± dipyridamole or clopidogrel + warfarin

Coronary obstruction : thrombolytic therapy, surgical or interventional procedures

Follow up

Subsequent follow up

- Echo 2 weeks after hospital discharge

- Echo 6-8 weeks after onset of illness

If both are normal, no more follow up is needed, if not, echo, every 1-2 yrs

Long-term follow up

1) Patients with no evidence of coronary artery abnormalities:

- No need for aspirin or other antiplatelet medications beyond 2-3 mo

- No restriction of physical activity

2) Patients with transient coronary ectasia or aneurysms:

- 3-5mg/kg/d aspirin until resolution

- followed with echo Q 1-2 yrs and stress testing Q 3-5 yrs

- No need for physical activity restriction unless abnormal stress test

Long-term follow up

3) Patients with persistent small to medium solitary coronary aneurysm:

- **Maintain on daily low dose aspirin**
- **Annual echo follow up**
- **Stress testing Q 1-2 yrs**
- **Angiography if stenosis is suggested**
- **Allowable physical activity**

4) Patients with giant or multiple smaller aneurysms:

- **Aspirin 3-5mg/kg/d ± dipyridamol 3-4mg/kg/d TDS or clopidogrel**
- **Warfarin to maintain INR at 2-2.5**
- **Cardiac evaluation Q 6-12 mo**
- **Periodic stress testing**
- **Angiography after the acute stage of disease**
- **Physical activity should be regulated**

5) Patients with coronary obstruction:

- **Balloon angioplasty**
- **CABG**
- **Cardiac transplantation**

Prognosis

- 20-25% of untreated patients develop coronary abnormalities.
- 3% of patients receiving IVIG develop coronary abnormalities.
- 50% of children with small to medium coronary aneurysms 4-8 wks after onset, demonstrate regression by 2yrs.
- Patients with giant coronary aneurysms are at risk for stenosis and myocardial infarction

Thanks for your attention