KAWASAKI DISEASE

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Kawasaki disease is the 2nd commonest childhood febrile vasculitic illness after Henoch Schonlein purpura. However it is associated with significant morbidity and mortality because of its coronary sequelae, especially if diagnosis and treatment are delayed. It imposes challenge to practicing clinician because of its relatively non-specific clinical features particularly during early phase of illness and lack of specific laboratory test to confirm or exclude the diagnosis.

Contents

• Historic perspective
• Epidemiology
• Diagnostic criteria
• Laboratory findings
• Cardiovascular complications
• Atypical Kawasaki disease
• Poor prognostic factors
• Acute management
• Subsequent management
• Risk stratification
• Summary
Historic Perspective

Kawasaki’s disease was first described by Tomisaku Kawasaki in 1967. Initially it was thought to be a benign childhood febrile illness. In 1965, Noboru Tanaka discovered coronary artery thrombosis from autopsy of a child who died suddenly. He named this condition as “infantile polyarteritis nodosa”. Until 1970, 10 autopsy reports established clear link between coronary complications and Kawasaki disease. It was not until 1976 that people realized in fact, Kawasaki disease is what was previously known as infantile polyarteritis nodosa.

Epidemiology

The incidence of Kawasaki’s disease is 102 – 108 per 100 000 population below 5 years of age with a male to female ratio of 1.37 and occurring at peak age of 6 months old. It has a worldwide distribution but a higher prevalence among Asians. In developed countries, it has replaced acute rheumatic fever as the commonest acquired heart disease in children.

Clinical Features

There are 3 clinical phases of the disease

<table>
<thead>
<tr>
<th>Phase</th>
<th>Clinical features</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Fever, signs as in diagnostic criteria, myocarditis</td>
<td>1 to 2 weeks</td>
</tr>
<tr>
<td>Subacute</td>
<td>Defeverenese, periungual desquamation, thrombocytosis, coronary arteritis, acute myocardial infarction</td>
<td>2 to 4 weeks</td>
</tr>
<tr>
<td>Convalescence</td>
<td>Until ESR normalizes</td>
<td>4 to 8 weeks</td>
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</table>

The diagnosis is mainly clinical and there is no single diagnostic test available.

Diagnostic Criteria

Fever persisting at least 5 days + at least 4 of the following 5 principal features:

- Changes in extremities:
  - Acute: Erythema and edema of hands and feet
  - Convalescent: Membranous desquamation of fingertips
- Polymorphous exanthema
- Bilateral, painless bulbar conjunctival injection without exudate
- Changes in lips and oral cavity:
- Erythema and cracking of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
- Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral
Fewer than 4 principal criteria is needed if coronary artery disease is detected by echocardiography or coronary angiography

The diagnosis can be made before 5 days of fever by experienced clinicians.

**Characteristics of fever:**
- High spiking fever > 40° C
- Remittent
- Without treatment, fever may last for 2 - 4 weeks
- Frequently resolves within 1 - 2 days after high dose aspirin (100 mg/kg/day) or a single dose IVIG (2 gm/kg)

**Other useful features:**
- Striking irritability
- Indurated BCG scar
- Cardiovascular: myocarditis, pericarditis, valvular regurgitation, pericardial effusion, heart failure
- Central nervous: febrile convulsions, aseptic meningitis, encephalopathy, ataxia
- Abdomen: gastroenteritis, hydrops of gallbladder, paralytic ileus, jaundice
- Musculoskeletal: arthritis, arthralgia
- Genitourinary: urethritis, metritis, dysuria
- Pneumonitis
- Uveitis

**Laboratory Findings**

<table>
<thead>
<tr>
<th>Test</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>Mild normocytic normochromic anaemia, leukocytosis with left shift, thrombocytosis in subacute phase</td>
</tr>
<tr>
<td>ESR</td>
<td>Raised</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Raised</td>
</tr>
<tr>
<td>Liver functions test</td>
<td>Mild raised transaminases</td>
</tr>
<tr>
<td>Urine microscopy and biochemistry</td>
<td>Sterile pyuria, proteinuria</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Abnormal Q waves, prolonged PR and/or QT intervals, low voltage, ST-T wave changes</td>
</tr>
<tr>
<td>Chest Xray</td>
<td>Cardiomegaly if myocarditis is present</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Coronary artery aneurysm, pericardial effusion, decreased contractility, valvular regurgitation</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>Mononuclear pleocytosis</td>
</tr>
</tbody>
</table>

**Cardiovascular Complications**

**Coronary Artery Complications**
- Incidence of 24.6 % in untreated cases
• Primary pathology: acute vasculitis
• Saccular/ fusiform aneurysms usually develop between 18 and 25 days of illness
• 1 – 2 % fatality rate without treatment – myocardial infarction or rupture of aneurysm
• At 6 – 18 months, 49.3 % of initial coronary abnormalities will resolve
• Of those with persistent aneurysm
  – One half smaller aneurysm than before
  – One third has obstruction/ stenosis
  – Remainder has irregularities of coronary artery
• After 10 – 21 years
  – Ischaemic heart disease developed in 4.7%
  – Myocardial infarction occurred in 1.9%
  – Bypass surgery was required in 1.2%
  – Overall mortality 0.8%
• Giant coronary aneurysm
  – Defined as aneurysm with internal luminal diameter > 8 mm
  – More likely to thrombose, rupture or stenose
  – Less likely to resolve spontaneously
  – Overall incidence of 4.4%
  – 46% risk of complete obstruction over time
  – 60% risk of myocardial infarction
• Acute myocardial infarction
  – Most commonly occurs at 2 to 12 weeks of illness
  – Different symptomatology from adult
  – Non-specific signs and symptoms such as sudden unexplained shock, unrest, vomiting or abdominal pain
  – Chest pain is experienced only by older children

Non-coronary Complications
• Acute Myocarditis
  – Incidence of 50% during acute stage
  – Tachycardia in excess of degree of fever
  – ECG changes: prolonged PR interval, ST segment changes, ↓R wave voltage
  – Rarely causes congestive heart failure and cardiogenic shock
• Pericarditis
  – Incidence: 25% of cases during acute stage
  – Characterized by pericardial effusion, usually without causing haemodynamic disturbance
• Valvular diseases
  – Commonly mitral regurgitation
  – Incidence: 1.2 % of cases
• Systemic arteries aneurysms
  – Occurs in 2.2 % of patients
  – Most also have coronary aneurysm
− Common sites: renal, paraovarian/paratesticular, mesenteric, pancreatic, hepatic, iliac, splenic, axillary

**Atypical Kawasaki Disease**

This happens when fever is associated with less than 5 clinical criteria stated above. It also tends to occur in young infants especially below 6 months of age. Fever may be the only sole clinical manifestation of the illness. This group of children is more likely to develop coronary complications (20% vs 9%). Unfortunately, they are more likely to receive late treatment because of delay in diagnosis.

**Poor Prognostic Factors**

- Duration of fever > 16 days
- Recurrence of fever following period of no fever of more than 48 hours
- Arrhythmia other than 1st degree heart block
- Male gender
- Age < 1 year or > 10 years
- Cardiomegaly
- Low platelet, haematocrit, albumin level initially

**Acute Management**

1. **Intravenous immunoglobulin (IVIG)**

IVIG has been shown unequivocally in meta-analysis to reduce occurrence of coronary complications. The prevalence of coronary complications is highly dependent on total IVIG dose and not the aspirin dose. The optimal dose is 2 gm/kg. Single infusion (2 gm/kg over 10 hours) is superior to divided lower dose of IVIG (400 mg/kg per day for 4 consecutive days). However, divided lower dose should be considered in sick infant who cannot tolerate large volume load of single dose IVIG. IVIG treatment should be started early in the disease, preferably within the first 10 days of the illness. A second dose may be indicated in minority of cases in whom there has been primary treatment failure or recrudescence.

2. **Aspirin**

During the acute phase, a higher anti-inflammatory dose is used and has been shown to be better than the lower dose in reduction of duration of fever and length of stay. The following is the treatment schedule for aspirin.
- Start with 100 mg/kg/day in divided doses
- Once fever has settled and acute inflammatory markers have normalized, reduce to anti-platelet dose of 4 mg/kg/day single daily dose
3. Corticosteroid

The use remains controversial. Pulse methylprednisolone has been reported to be useful in IVIG resistant cases.

Subsequent Management

The following investigations are recommended at specific time intervals:

- **Acute inflammatory markers: FBC, ESR, CRP**
  - On admission
  - Before discharge
  - Between 2 to 4 weeks from initial presentation
  - Between 6 to 8 weeks from initial presentation
  - Thereafter on cardiologists’ discretion

- **Electrocardiography**
  - At diagnosis
  - Thereafter on cardiologist’s discretion

- **Echocardiography**
  - At diagnosis
  - Between 2 to 4 weeks from initial presentation
  - Between 6 to 8 weeks from initial presentation
  - Thereafter on cardiologist’s discretion

It is recommended that all vaccinations be deferred for at least 3 months if IVIG has been given for treatment.

Risk Stratification

Subsequent management strategy depends on presence and degree of severity of coronary artery complications. Every patient should be risk stratified according to following criteria into 5 risk levels:

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with no coronary artery changes on echocardiography at any stage of the illness</td>
</tr>
<tr>
<td>II</td>
<td>Patients with transient coronary artery ectasia (disappears during the acute illness) on echocardiography</td>
</tr>
<tr>
<td>III</td>
<td>Patients with a small to medium solitary coronary artery aneurysm on echocardiography or angiography</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with one or more giant coronary artery aneurysms or multiple small to medium aneurysms, without obstruction by echocardiography</td>
</tr>
<tr>
<td>V</td>
<td>Patients with coronary artery obstruction confirmed by angiography</td>
</tr>
</tbody>
</table>
## Management Based on Risk Stratification

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Pharmacologic therapy</th>
<th>Physical activity</th>
<th>Follow-up and diagnostic testing</th>
<th>Invasive testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None beyond initial 6 to 8 weeks</td>
<td>No restrictions beyond initial 6 to 8 weeks</td>
<td>None beyond 1st year unless cardiac disease suspected</td>
<td>None recommended</td>
</tr>
<tr>
<td>II</td>
<td>None beyond initial 6 to 8 weeks</td>
<td>No restrictions beyond initial 6 to 8 weeks</td>
<td>None beyond 1st year unless cardiac disease suspected</td>
<td>None recommended</td>
</tr>
<tr>
<td>III</td>
<td>3 to 5 mg/kg aspirin per day, at least until abnormalities resolve</td>
<td>For patients in 1st decade of life, no restriction beyond initial 6 to 8 weeks. For patients in 2nd decade, physical activity guided by stress testing every other year. Competitive contact athletics discouraged</td>
<td>Annual follow-up with echocardiogram ± ECG in 1st decade of life</td>
<td>Angiography, if stress testing or echocardiogram suggests stenosis</td>
</tr>
<tr>
<td>IV</td>
<td>Long-term aspirin (3 to 5 mg/kg per day) ± warfarin</td>
<td>For patients in 1st decade of life, no restriction beyond initial 6 to 8 weeks. For patients in 2nd decade, annual stress testing guides recommendations. Strenuous athletics are strongly discouraged</td>
<td>Annual follow-up with echocardiogram ± ECG ± chest x-ray ± additional ECG at 6-month intervals. For patients in 1st decade of life, pharmacologic stress testing should be considered</td>
<td>Angiography, if stress testing or echocardiography suggests stenosis</td>
</tr>
<tr>
<td>V</td>
<td>Long-term aspirin (3 to 5 mg/kg per day) ± warfarin. Use of calcium channel blockers should be considered to reduce myocardial oxygen consumption</td>
<td>Contact sports, isometrics &amp; weight training should be avoided. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan</td>
<td>Echocardiogram and ECG at 6-month intervals and annual Holter and stress testing</td>
<td>Angiography for some patients to aid in selecting therapeutic options. Repeat angiography with new-onset or worsening ischemia</td>
</tr>
</tbody>
</table>

### Summary

Kawasaki disease has become an important acquired heart disease and vasculitic syndrome during childhood. Coronary artery complications are responsible for majority of its morbidity and mortality. Diagnosis remains a clinical one based on a set of clinical criteria; however, atypical presentation is not uncommon especially among younger age group. Use of IVIG has reduced the rate of coronary sequelae significantly even though there is still a role for aspirin. Long term follow-up and treatment are required for those with persistent coronary abnormalities.