Kawasaki Disease

Synonyms: Kawasaki's disease, Kawasaki/Kawasaki's syndrome, mucocutaneous lymph node syndrome, infantile periarteritis nodosa, infantile polyarteritis nodosa.

Kawasaki disease is an idiopathic self-limiting systemic vasculitis that most often affects children in the age range 6 months to 5 years. It predominantly affects children of Asian origin, particularly Japanese and Chinese populations (possibly because of genetic susceptibility) but there is an appreciable worldwide incidence. It was first described in 1967 by Tomisaku Kawasaki, a Japanese paediatrician.

It was originally thought to be a troubling but benign illness but it was later realised that deaths and significant morbidity occur through its major complication of coronary artery aneurysm formation. It has taken over from rheumatic fever as the most common cause of acquired childhood heart disease in the developed world.[1] Prior to its delineation, cases had been described and classified on histological grounds as infantile polyarteritis/periarteritis nodosa. Early diagnosis and early treatment are now strongly advocated to reduce complications and have been shown to do so.

Its characteristic features are outlined below:

### Classical features of Kawasaki disease
- Fever lasting ≥5 days.
- Marked irritability of the child.
- Erythema, swelling and desquamation affecting the skin of the extremities.
- Bilateral conjunctivitis.
- Rash.
- Inflammation of the lips, mouth and/or tongue.
- Cervical lymphadenopathy.

### Epidemiology[1]

The highest annual incidence is thought to occur in Japan at 239 cases per 100,000 children aged under 5 years. [2] The incidence appears to be rising year on year in Japan.

Analysis of hospital statistics in England has shown an incidence of 8.39 per 100,000 of children aged under 5 years. [3] The higher incidence in Northeast Asians persists after migration to countries with low incidence.

There is clear variation in incidence with ethnicity, with a bias towards East Asian children. A study from Hawaii showed an annual incidence of 210 per 100,000 Japanese American children under 5 years, compared to 13 per 100,000 white children. [2]

The diagnosis is frequently missed, as the early stages mimic many viral infections. A study into diagnosis by UK GPs demonstrated a delay of more than 10 days between presentation and admission in 7% of cases. [4] At presentation, few typical clinical features were present.

85% of affected children are under the age of 5, with a peak incidence between the ages of 18 and 24 months.

It is more common in boys.
Aetiology and pathophysiology\[1\]
These remain a mystery, although a combination of an infective trigger and genetic susceptibility seems likely. Seasonal differences and epidemics seem to suggest an infective component but no single pathogen has yet been identified. A genetic component to susceptibility is assumed from the much higher incidence in Asian children, particularly those from Japan or Korea. It is assumed that an infective agent (not necessarily a single one) triggers an abnormal immune response in certain individuals. The condition is caused by an autoimmune-mediated systemic vasculitis that affects small- and medium-sized arteries.

Presentation\[1, 5\]
Assess children with fever lasting more than five days for Kawasaki disease.\[6\]

Symptoms
The usual presenting feature is a fever of abrupt onset. The child tends to be very irritable and unwell when febrile, often out of proportion to the severity of the fever. Most consider that the fever must have been present for at least five days for Kawasaki disease to be diagnosed; however, experienced clinicians may make the diagnosis earlier in its course, if there are other classical features. As well as fever of 39°C or more, there must be at least four of the following to fit the diagnostic criteria (or echocardiographic evidence of coronary artery aneurysms):
- Inflammation and irritation of the lips, mouth and/or tongue (eg, cracked lips, strawberry tongue, inflamed mucosa of mouth or pharynx).
- Erythema, oedema and/or desquamation of the extremities.
- Bilateral dry conjunctivitis.
- Widespread non-vesicular rash.
- Cervical lymphadenopathy >1.5 cm in size.

These features may occur in turn, so some may have gone at the time of presentation; therefore, a careful history is important. Incomplete Kawasaki disease is the term given to those with fever but without enough other features to fit the diagnostic criteria. This is common - 15-20% of cases - and comes with an increased risk of complications, probably due to diagnostic delay.

Other possible features include lethargy, urethritis, diarrhoea, vomiting, abdominal pain, myalgia, arthralgia and arthritis, along with other less common features listed in the ‘Subsidiary features of the disease’ section below.

Signs
- The lips typically become erythematous or fissured, along with inflamed oral mucosa and the presence of a ‘strawberry tongue’ - so-called because it is extremely erythematous with prominent papillae.
- The rash is described as a polymorphic exanthem and comes on within 3-5 days of the onset of fever. It usually begins with nonspecific erythema of the soles, palms and perineum, spreading to involve the trunk and the rest of the extremities. It is often itchy and variable in appearance but is never vesiculo-bullous. It is usually marked red and may appear macular, morbilliform, papular, scarlatiniform, urticarial, akin to erythema multiforme or be made up of very many tiny micropustules.
- Desquamation may affect the perineal area, moving to the fingers and then the toes. In the extremities, it usually begins in the periungual region.
- The hands and feet often become red and swollen and tender before desquamation begins.
- The conjunctivitis is never associated with exudate, is bilateral and tends to spare the perilimbual area.
- Cervical lymphadenopathy is usually unilateral, non-tender and affects the anterior cervical chain.
- Cardiovascular signs are usually nonspecific. Tachycardia, a hyperdynamic precordium, a gallop rhythm or a flow murmur may be present; however, these signs are not unusual in febrile patients without Kawasaki disease. There are occasionally signs of valvular incompetence.
- Other possible signs include:
  - Neck stiffness due to aseptic meningitis.
  - Hepatomegaly and jaundice.
Phases of the illness
The disease typically follows three phases, as outlined in the table below:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time from fever onset</th>
<th>Predominant features</th>
</tr>
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<tbody>
<tr>
<td>Acute</td>
<td>1-2 weeks</td>
<td>• Highly febrile.</td>
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<td>• Very irritable.</td>
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<td></td>
<td>• Toxic-appearing.</td>
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<td></td>
<td></td>
<td>• Oral changes rapidly following.</td>
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<td></td>
<td></td>
<td>• Oedema and erythema of feet.</td>
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<td></td>
<td></td>
<td>• Rash especially common in the perineal area.</td>
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<tr>
<td>Subacute</td>
<td>2-8 weeks</td>
<td>• Gradual improvement.</td>
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<tr>
<td></td>
<td></td>
<td>• The fever settles.</td>
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<tr>
<td></td>
<td></td>
<td>• Desquamation of the perineum, palms, soles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Arthritis, arthralgia.</td>
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<tr>
<td></td>
<td></td>
<td>• Thrombocytosis.</td>
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<tr>
<td></td>
<td></td>
<td>• Coronary artery aneurysms.</td>
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<td></td>
<td></td>
<td>• Myocardial infarction.</td>
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<tr>
<td>Convalescent</td>
<td>Months to years</td>
<td>• Resolution of remaining symptoms.</td>
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<td></td>
<td></td>
<td>• Laboratory values return to normal.</td>
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<td>• Aneurysms may resolve or persist.</td>
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<td>• Beau's lines.</td>
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<td>• Cardiac dysfunction and myocardial infarction may still occur.</td>
</tr>
</tbody>
</table>

Subsidiary features of the disease
- Cardiovascular - pancarditis, aortic or mitral incompetence.
- Gastrointestinal - hydrops of gallbladder, jaundice, diarrhoea.
- Blood - mild anaemia.
- Renal - sterile pyuria, mild proteinuria.
- CNS - aseptic meningitis.
- Musculoskeletal - arthritis, arthralgia.
- Others - anterior uveitis, BCG-site inflammation.[7]

Differential diagnosis
- Measles.
- Rubella.
- Infectious mononucleosis.
- Enteroviruses.
- Parvovirus B19 infection.
- Any bacterial infection - especially staphylococcal and streptococcal infections causing staphylococcal scalded skin syndrome, toxic shock syndrome and scarlet fever.
- Toxic epidermal necrolysis.
- Other drug reactions, particularly erythema multiforme and Stevens-Johnson syndrome.
- Meningitis or encephalitis.
- Tick-borne disease such as Rocky Mountain spotted fever and relapsing fever.
- Mercury toxicity (acrodynia).
- Toxoplasmosis.
Investigations

- There is no diagnostic test for the condition. Diagnosis is made clinically and depends on the presence of the diagnostic features described above.
- Urinalysis may show sterile pyuria ± proteinuria.
- FBC during the acute phase usually shows leukocytosis and neutrophilia, and acute-phase reactant markers such as ESR and CRP are usually elevated.
- Platelets are elevated and there may be a marked thrombocytopenia that develops throughout the second and third weeks of the illness.
- LFTs may show elevation of the transaminases and bilirubin.
- Abdominal ultrasound can show evidence of gallbladder distension.
- ECG may show a range of conduction abnormalities due to carditis.
- Echocardiography is essential. It can reveal dilatation and aneurysms of the coronary arteries, as well as allowing assessment of the pericardium and left ventricular/valvular function. Serial echocardiography is often needed to detect occult coronary artery disease as the illness evolves.

Management

Management[1, 5, 8]

Clinical Editor’s notes (August 2017)

Dr Hayley Willacy would like to draw your attention to this American paper that covers new information on epidemiology, genetics, pathogenesis, pathology, natural history, and long-term outcomes[9]. An updated algorithm defines the additional information needed to make the diagnosis when classic clinical criteria are absent. Although intravenous immune globulin is the mainstay of treatment, the role for additional therapy in certain patients is covered. Approximately 10% to 20% of patients do not respond to initial intravenous immune globulin, and recommendations for additional therapies are provided.

- Children with the condition are usually cared for as inpatients on paediatric or paediatric-cardiology units and put on bed rest, due to the risk of myocardial events.
- The mainstays of management are the use of aspirin and intravenous immunoglobulin (IVIG) to reduce fever and myocardial inflammation and to prevent or ameliorate cardiac sequelae (the main cause of morbidity and mortality associated with the condition).
- In some countries, corticosteroids are used additionally in severe cases.
- Follow-up echocardiography is useful in determining whether or not there have been any coronary artery complications.
- Percutaneous coronary intervention and coronary artery bypass grafting may be indicated in very severe cases with cardiac complications.

Aspirin

The routine use of aspirin in the management of febrile children is not recommended due to the danger of Reye’s syndrome.

However, in Kawasaki disease, the antiplatelet and antipyretic effect of the drug provides the rationale for its use. The drug is used widely in a variety of high-dose and low-dose regimens, both in the acute and subsequent phases, and as long-term prophylaxis against coronary events in those who have coronary artery aneurysms. There is a scant evidence base to support its use and little useful research to decide on the optimal regimen. Usually higher doses are used in the acute inflammatory phases, followed by a lower antiplatelet dose in later phases.

A Cochrane review in 2006 concluded that until good-quality randomised controlled trials are carried out, there is insufficient evidence to indicate whether children with Kawasaki disease should continue to receive aspirin as part of their treatment regimen.[10]

IVIG

IVIG is the mainstay of treatment. It has been shown to reduce the incidence of coronary artery aneurysms from about 25% in the untreated to less than 5%. 2g/kg as a single infusion over 12 hours is the standard regime.

IVIG resistance is a problem in as many as 20% of cases and these children are at risk of cardiac complications unless they receive additional therapy. This may then be in the form of further IVIG, or corticosteroids, or a number of other possibilities.

Children treated with IVIG should have immunisations with live vaccines (eg, MMR) delayed for 3-11 months after treatment (UK recommendation is 3 months).
Adjunctive therapy in refractory cases

The following agents have been used in refractory cases:

- **Corticosteroids.** These have traditionally been avoided, as early studies suggested they increased the complication rate. However, a meta-analysis in Japan showed addition of prednisolone in a dose of 2 mg/kg/day to IVIg treatment reduced coronary complications. Evidence is not yet convincing enough for steroids to be used routinely as part of primary treatment but they may have a useful role in those with IVIg resistance. Research continues on how to predict this population.\(^1\) Evidence is not yet convincing enough for steroids to be used routinely as part of primary treatment but they may have a useful role in those with IVIg resistance. Research continues on how to predict this population.

- **Anti-tumour necrosis factor (anti-TNF)-alpha therapies:**
  - Infliximab (monoclonal antibody acting as TNF-alpha antagonist).\(^2\)
  - Etanercept (a soluble TNF-alpha receptor).\(^3\)

- **Other immunosuppressive therapy:**
  - Ciclosporin.
  - Cyclophosphamide.
  - Low-dose methotrexate.\(^4\)

- **Plasma exchange.**

Management of coronary artery aneurysms

This is also an area of uncertainty. A paediatric cardiologist should be involved if there is evidence of dilation of coronary arteries. Regular echocardiograms and tests of cardiac function are required.

Percutaneous coronary intervention may be required for those at high risk of cardiac ischaemia, such as:

- Intracoronary thrombolysis
- Balloon angioplasty
- Cardiac stents
- Ablation therapy

Occasionally, coronary artery bypass surgery may be needed.

Long term antiplatelet/anticoagulant therapies will be required, usually aspirin with either warfarin or low molecular weight heparin.

Complications

- Sudden cardiac death.
- Myocardial infarction.
- Coronary artery aneurysms
- Coronary artery aneurysm rupture.
- Pericarditis.
- Myocarditis.
- Cardiac valvular disease.
- Cardiac dysrhythmia.
- Heart failure.
- Acute arthritis.
- Dehydration in the acute phase of the illness.
- Recurrence of the condition (estimated to affect less than 1%).\(^5\)

Prognosis\(^6\)

- Prognosis depends upon the degree of cardiac involvement.
- Although the majority of patients do well and do not experience major complications, up to 50% show echocardiographic evidence of cardiac impairment and mild mitral regurgitation.
- 15-25% of untreated patients will experience coronary artery aneurysms but this figure is much lower if early diagnosis and therapy are achieved. 1% become giant aneurysms (>8 mm internal diameter).\(^7\)
- Most (50-70%) coronary artery aneurysms regress after a period of 1-2 years, although giant aneurysms never resolve entirely and have a worse prognosis.
- Mortality varies between populations and treating centres but is in the range 0.08-3.7%. In the UK there were no reported deaths from Kawasaki disease in the period January 2013 to January 2015 in an analysis by the British Paediatric Surveillance Unit (BPSU).\(^8\)
- Follow-up in later life is recommended. Kawasaki disease is a relatively new disease, and the long-term cardiac implications are not yet fully known.
- Kawasaki disease is not contagious.

Further reading & references

6. Fever in under 5s - assessment and initial management; NICE Guideline (updated August 2017)
16. BPSU Annual Report 2013-2014; British Paediatric Surveillance Unit

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