



# Kawasaki Disease: A comprehensive approach to its signs, symptoms, causes and treatment for further studies

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## Abstract

Kawasaki Disease is a small-to-medium-vessel vasculitis that preferentially affects children. Kawasaki Disease can occur in adults, but the presentation may differ from that observed in children. Typical findings in both adults and children include fever, conjunctivitis, pharyngitis, and skin erythema progressing to a desquamating rash on the palms and soles. Adults more frequently present with cervical adenopathy (93% of adults vs. 15% of children), hepatitis (65% vs. 10%), and arthralgia (61% vs. 24–38%). In contrast, adults are less frequently affected by meningitis (10% vs. 34%), thrombocytosis (55% vs. 100%), and coronary artery aneurysms (5% vs. 18–25%). We report a case of acute Kawasaki Disease in a 24-year-old man who presented with rash, fever, and arthritis. He was successfully treated with high-dose aspirin and intravenous immunoglobulin (IVIG). Our case highlights the importance of considering Kawasaki Disease in adults presenting with symptoms commonly encountered in a general medical practice.

**Key words:** Kawasaki Disease, adult, coronary artery aneurysms, vasculitis, adenopathy, arthritis, mucocutaneous lymph node syndrome

## Introduction

Kawasaki disease (KD) is named after the Japanese pediatrician Tomisaku Kawasaki who in 1967 described 50 cases of infants with persistent fever, accompanied by rash, lymphadenopathy, edema, conjunctival injection, redness and cracking of the lips, "strawberry tongue," and convalescent desquamation. Today KD is understood as a rash/fever illness of early childhood in which coronary artery aneurysms (CAA), sometimes fatal, may develop in up to 25 percent of untreated children.

The incidence is highest in Japan with an annual rate of 130-140/100,000 children under 5 years of age. In comparison, incidence for the continental U.S. varies between 9 and 20/100,000 children under 5 years of age and for Japanese Americans living in Hawaii between 120 and 130/100,000 in children under 5 years of age. Because its etiologic agent(s) and pathophysiological mechanisms remain unknown, and because there is no diagnostic laboratory test for KD, diagnosis relies on the observation and recognition of clinical signs that comprise the KD case definition. With the establishment of intravenous immunoglobulin (IVIG) as an effective therapy, prompt diagnosis has become essential for timely therapy to ensure a good cardiac outcome.

Although researchers have attempted to uncover the etiology of KD since the 1960s, we appear to be no closer to an answer. Among those who assume there is an infectious agent, disagreement continues over whether the agent is bacterial or viral and whether or not it acts as a super-antigen. Immune response remains a crucial arena of investigation; yet no robust hypothesis has convincingly linked the sign complex and immune cascade with the development of CAA.

Kawasaki syndrome is a potentially fatal inflammatory disease that affects several organ systems in the body, including the heart, circulatory system, mucous membranes, skin, and immune system. It occurs primarily in infants and children but has also been identified in adults as old as 34 years.

Kawasaki syndrome, also called mucocutaneous lymph node syndrome (MLNS), is an inflammatory disorder with potentially fatal complications affecting the heart and its larger arteries. Nearly twice as many males are affected as females. Although persons of Asian descent are affected more frequently than either black or white individuals, there does not appear to be a distinctive geographic pattern of occurrence. Eighty percent of cases involve children under the age of four. Although the disease usually appears in individuals, it sometimes affects several members of the same family and occasionally occurs in small epidemics.

## History

Kawasaki syndrome (KS), also known as Kawasaki disease, is an acute febrile illness of unknown etiology that primarily affects children younger than 5 years of age. KS was first described in Japan by Tomisaku Kawasaki in 1967, and the first cases outside of Japan were reported in Hawaii in 1976.

KS occurs worldwide, with the highest incidence in Japan, and it most often affects boys and younger children. KS may have a winter-spring seasonality, and community-wide outbreaks have been reported occasionally. In the continental United States, population-based and hospitalization studies have estimated an incidence of KS ranging from 9 to 19 per 100,000 children younger than 5 years of age. Approximately 4248 hospitalizations with KS, of which 3277 (77%) were for children under 5 years of age, were estimated among children younger than 18 years of age in the United States in the year 2000. In 2006, the number of hospitalizations with KS was 5523 (standard error [SE] 289) and the percentage of children under 5 years of age remained the same.

## Classification

- **Acute stage (weeks 1 to 2)**

Fever, irritability, conjunctivitis, rash, mucosal erythema, possible myocarditis, and pericarditis.

- **Subacute stage (weeks 2 to 4)**

Fever, rash and lymphadenopathy have resolved; if fever persists there is an increased risk of cardiac complications; persistent irritability, poor appetite, and conjunctival injection; desquamation of extremities begins at this stage

Cardiac abnormalities (coronary artery ectasia or aneurysms) may develop during this stage.

- **Convalescent (weeks 4 to 8)**

All signs of inflammation have disappeared and acute phase markers normalize.

If present, coronary artery ectasia or aneurysms may persist and enlarge.

- **Chronic stage (variable)**

If present, coronary artery dilation may resolve

However, coronary artery aneurysms may persist through adulthood. Such patients are at risk of subsequent coronary artery thrombosis, rupture and myocardial infarction.

## Signs and symptoms

- fever,
- reddening of the eyes without pus,
- cracked and inflamed lips and mucous membranes of the mouth with an inflamed "strawberry" tongue,
- ulcerative gum disease (gingivitis),
- swollen lymph nodes in the neck (cervical lymphadenopathy),
- joint pain often on both sides of the body,
- irritability,
- cough and runny nose,
- and a rash that is raised and bright red, especially on the palms and soles.



(Figure 1)

**Reddening, swelling or peeling of the hands and feet**



(Figure 2)

**Red tongue and prominent papillae ("strawberry tongue")**



(Figure 3)

**Conjunctivitis without mucopurulent discharge**



(Figure 4)

**Red and sore eyes, lips, and mouth**

The rash appears in a glove-and-sock fashion over the skin of the hands and feet. The rash becomes hard, swollen (edematous), and then peels off.

Kawasaki disease often begins with a high and persistent fever greater than 102 °F, often as high as 104 °F. A persistent fever lasting at least 5 days is considered a classic sign. The fever may last for up to 2 weeks and does not usually go away with normal doses of acetaminophen (Tylenol) or ibuprofen.

Other symptoms often include:

- Extremely bloodshot or red eyes (without pus or drainage)
- Bright red, chapped, or cracked lips
- Red mucous membranes in the mouth
- Strawberry tongue, white coating on the tongue, or prominent red bumps on the back of the tongue
- Red palms of the hands and the soles of the feet
- Swollen hands and feet
- Skin rashes on the middle of the body, NOT blister-like
- Peeling skin in the genital area, hands, and feet (especially around the nails, palms, and soles)
- Swollen lymph nodes (frequently only one lymph node is swollen), particularly in the neck area
- Joint pain and swelling, frequently on both sides of the body

Additional symptoms may include:

- Irritability
- Diarrhea, vomiting, and abdominal pain
- Cough and runny nose

## Signs and tests

No tests specifically diagnose Kawasaki disease. The diagnosis is usually made based on the patient having most of the classic symptoms.

However, some children may have a fever lasting more than 5 days, but not all of the classic symptoms of the disease. These children may be diagnosed with atypical Kawasaki disease. Therefore, all children with fever lasting more than 5 days should be evaluated, with Kawasaki disease considered as a possibility. Early treatment is essential for those who do have the disease.

The following tests may be performed:

- Chest x-ray
- Complete blood count
- C-reactive protein (CRP)
- Echocardiogram
- Electrocardiogram
- ESR
- Serum albumin
- Serum transaminase
- Urinalysis - may show pus in the urine or protein in the urine

Procedures such as ECG and echocardiography may reveal signs of myocarditis, pericarditis, arthritis, aseptic meningitis, and inflammation of the coronary arteries.

## Causes

Experts do not really know what causes the disease. We are pretty sure it is a virus because of the characteristics of many of the symptoms. It is not a contagious disease, however so, it is unlikely to have a virus. Some studies indicate that perhaps Kawasaki disease is caused by an abnormal reaction to some common virus which would not bother most people. Some say it is an autoimmune disorder - the body's immune system attacks its own good tissue as if it were a pathogen (organism that causes disease). Unfortunately, there is no clear evidence of any cause for Kawasaki disease.

## Treatment

Because of the risk of complications, Kawasaki disease is usually treated in hospital. Treatment should be done promptly for faster recovery and to reduce the risk of complications.

Two main medicines for Kawasaki disease treatment:

- Aspirin - children under 16 should not be given aspirin. However, it is prescribed if a child has Kawasaki disease. Children with Kawasaki disease have a very high blood platelet count, making them very susceptible to blood clots forming in their bloodstream. Aspirin helps prevent blood clots, as well as reducing the fever, rash and joint inflammation.

For aspirin-therapy to be effective the child will normally require a high dose. It is important that the child is checked and monitored closely to make sure no undesirable side effects occur. Aspirin therapy may continue for several weeks after the child has recovered from symptoms.

- Gamma globulin - these are cells in the blood which help fight infection (antibodies). Gamma globulin is administered intravenously (through a vein in the child's arm). Symptoms tend to improve rapidly; within 24 hours of administering gamma globulin.

If there are any indications of heart problems the doctor may order follow-up tests, usually 6 to 8 weeks after symptoms started. If the child develops continuing heart problems the doctor may refer the child to a pediatric cardiologist - a doctor specialized in diagnosing and treating childhood heart problems. The following may be prescribed or ordered:

- Anticoagulant medications - examples may include warfarin, heparin or aspirin. These drugs prevent the undesirable formation of blood clots.
- Coronary artery angioplasty - this procedure opens up an artery that has narrowed by inflating a small balloon inside the artery which squashes a clot against the wall of the blood vessel.
- Stent - a stent may be placed in the clogged artery to help prop it open, reducing the risk of it becoming blocked again. A stent placement is often done along with an angioplasty.

Coronary artery bypass graft - blood flow is rerouted round a diseased coronary artery by grafting a section of blood vessel from the chest, arm or leg to use as the alternate route. The bypass effectively goes around the blocked area of the artery, allowing blood to pass through into the heart.

Children with Kawasaki disease are admitted to the hospital. Treatment must be started as soon as the diagnosis is made to prevent damage to the coronary arteries and heart.

Intravenous gamma globulin is the standard treatment. It is given in high doses. The child's condition usually greatly improves within 24 hours of treatment with IV gamma globulin.

High-dose aspirin is often given along with IV gamma globulin.

Even when they're treated with aspirin and IV gamma globulin, up to 25% of children may still develop problems in their coronary arteries. Some research has suggested that adding steroids to the usual treatment routine may improve a child's outcome continued for several months.

Information regarding the utility of IVIG and aspirin therapy is based on research performed in children, as cases of acute adult Kawasaki Disease are extremely rare. In children, IVIG reduces the incidence of coronary artery aneurysms if given within the first 10 days of disease onset. IVIG may help shorten disease duration even if started after the acute phase. The standard of care for children with acute Kawasaki Disease is a single 2-gm/kg infusion of IVIG along with 80–100 mg/kg/day of aspirin in 4 divided doses. Once the fever resolves, the aspirin may be decreased to 3–5 mg/kg/day. In patients with coronary artery aneurysms, aspirin should be continued until 2 years after the aneurysms resolve. If aneurysms do not resolve, then aspirin therapy is recommended indefinitely to prevent coronary artery thrombosis. Unlike IVIG, aspirin does not decrease the formation rate of coronary aneurysms.

Initial trials of IVIG therapy used a low dose administered over 4 days. In a pivotal trial, aspirin monotherapy was compared to 400 mg/kg/day of IVIG plus aspirin in 85 children with Kawasaki Disease. Children receiving IVIG enjoyed a significant reduction in the incidence of coronary artery aneurysms (15% vs. 42%,  $p < .01$ ). Similarly, another trial randomized 75 children to aspirin and IVIG (400 mg/kg/day for 4 days) and 78 children to aspirin monotherapy. Two weeks into the trial, 23% of the aspirin monotherapy group and 8% of the IVIG group had coronary artery aneurysms. At 7 weeks, 18% of the aspirin monotherapy group and 4% of the IVIG group had coronary artery aneurysms, suggesting a significant decrease in incidence of coronary artery aneurysms with IVIG therapy.

A more recent trial suggested that a single infusion of IVIG (2 g/kg) may accelerate resolution of inflammation compared to the 4-day regimen. Patients receiving 400 mg/kg/day for 4 days were almost twice as likely to have coronary artery aneurysms than those receiving a single 2-gm/kg dose (14 of 252 patients vs. 6 of 254 patients,  $p = .067$ ). As a result, the higher single dose has become the current standard of care for children with acute Kawasaki Disease. Although case reports describe benefit when adults with Kawasaki Disease receive IVIG, there are no controlled studies regarding the optimal dose, timing, or clinical benefit of IVIG therapy in adults. Potential risks of IVIG therapy include infusion reactions, volume overload, and osmotic nephropathy.

Surprisingly, corticosteroid therapy is not recommended for initial management of Kawasaki Disease, although a recent meta analysis reports a reduction in the rate of coronary artery aneurysms with its use. In 92 patients with Kawasaki Disease, aneurysms developed in 64.7% of the patients treated with steroids, 20% of those treated with antibiotics, and 11% of those treated with aspirin, raising concern that corticosteroids enhance the formation of coronary artery aneurysms. In a prospective randomized trial comparing aspirin and IVIG with or without corticosteroid therapy, patients receiving steroids enjoyed more rapid resolution of fever and shorter hospitalization, but no significant decrease in the rate of coronary aneurysms. A recent meta analysis of 862 children reported fewer coronary artery aneurysms in patients treated with corticosteroids.

## Conclusion

Kawasaki disease is a multi-system disease of unknown etiology with a characteristic presentation. However, it is a condition that may mimic other systemic diseases with multi-organ involvement and the clinician must investigate appropriately.

The mortality is usually associated with the cardiovascular system, but severe involvement of other organs may occur. The very long-term outlook for children with a history of KD remains unknown, and in Japan a national registry, currently with 6500 children entered, has been established to follow these children longitudinally. It will be particularly important to demonstrate whether there is a significantly increased risk of cardiovascular disease in later life, both in those with and without cardiac involvement during the acute illness.

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