CME

FIGURE 1. Conjunctivitis with limbic sparing is a diagnostic criterion for Kawasaki disease

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Kawasaki disease: Shedding light on a mysterious diagnosis

Jana Galuppo, PA-C; Alexandra Kowker, PA-C; Jenna Rolfs, PA-C; Joyce Nicholas, PhD; Eric Schmidt, PhD

ABSTRACT

Kawasaki disease is an acute systemic febrile vasculitis of medium and small arteries, most often occurring in children under age 5 years. This condition is the most common cause of acquired heart disease in children in the developed world. The cause is unclear but is thought to be a hyperimmune reaction to an infectious agent. Diagnosis is clinical; the classic presentation includes persistent fever, lymphadenopathy, oral mucosal changes, conjunctivitis, and rash. Although the disease technically is self-limiting, treatment with IV immunoglobulin (IVIG) and high-dose aspirin is necessary to prevent cardiac complications, such as coronary artery aneurysm, pericarditis, or myocarditis. This article reviews the pathophysiology, clinical presentation, diagnosis, and treatment of Kawasaki disease.

Keywords: Kawasaki disease, autoimmune, vasculitis, coronary artery aneurysm, pediatrics, CRASH and Burn

Learning objectives

- Describe the epidemiology and risk factors for Kawasaki disease.
- Discuss the clinical presentation of Kawasaki disease.
- Outline the typical treatment for Kawasaki disease.

In the early 1960s, Japanese pediatrician Tomisaku Kawasaki saw nearly 50 cases of a novel illness consisting of high fever, a desquamating rash, conjunctivitis, and lymphadenopathy.[1] This collection of self-limiting symptoms was initially called mucocutaneous lymph node syndrome and today most know it as Kawasaki disease. The cause of this disease is not yet fully elucidated, but advances in medicine have led to the understanding of Kawasaki disease pathophysiology, treatment, and complications that can occur if it is not treated.[2,3]

Kawasaki disease is an acute systemic febrile illness that causes vasculitis of the small- and medium-sized arteries, most notably the coronary arteries.[4] Most often seen in

At the time this article was written, **Jana Galuppo** and **Alexandra Kowker** were students in the PA program at the University of Lynchburg in Lynchburg, Va. Ms. Galuppo now practices at Centra Medical Group Neurology Center in Lynchburg, Va. Ms. Kowker practices in pediatrics at Johnson Health Center in Lynchburg, Va. At the University of Lynchburg, Jenna Rolfs is program director and an assistant professor, **Joyce Nicholas** is director of evaluation, assessment, and compliance and a professor, and **Eric Schmidt** is an assistant professor. The authors have disclosed no potential conflicts of interest, financial or otherwise.

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Key points

- Kawasaki disease is an acute, self-limiting vasculitis most often diagnosed in children of Northeast Asian descent who are under age 5 years.
- The cause may be a hyperimmune reaction to a virus, causing neutrophilic and lymphocytic infiltration of small- to medium-sized arteries, acute vascular inflammation, and vascular necrosis.
- Diagnosis is clinical but symptoms often mimic other viral processes and can lead to delayed or missed diagnosis.
- The absence of coronary vasculitis on echocardiogram does not rule out Kawasaki disease.
- IVIG and aspirin are the mainstays of treatment and should not be delayed.

children under age 5 years, Kawasaki disease has overtaken rheumatic heart disease as the most common cause of acquired heart disease in children in the developed world.[4] Kawasaki disease is a clinical diagnosis and initially mimics a viral syndrome, making recognition difficult, especially in the early days of the disease. Diagnosis is crucial, as any delay in treatment could allow the development of coronary artery aneurysms that may result in myocardial infarction, the need for coronary artery bypass or heart transplant, and in some cases, death.[5]

CAUSE

The cause of Kawasaki disease is still largely unknown. Although no specific pathogens have been linked to Kawasaki disease, the prevailing theory is that it is a hyperimmune reaction to a virus.[2,6] Supporting this theory are several commonalities seen in patients, including a history of viral exposure, seasonality, familial clustering, and young age.[7] Most patients are diagnosed with a viral illness before developing Kawasaki disease or have typical viral symptoms at the time of diagnosis, such as cough, rhinorrhea, or diarrhea.[4] Additionally, 60% of patients have a history of contact with persons affected by febrile, respiratory, or gastrointestinal illness.[4] Peak incidence of Kawasaki disease in the northern hemisphere is in the winter and spring, with declining rates in the fall.[8] The disease has been found to cluster within families. The age distribution (6 months to 2 years) coincides with the time that children are more susceptible to infectious disease because their immune systems are still developing.[4]

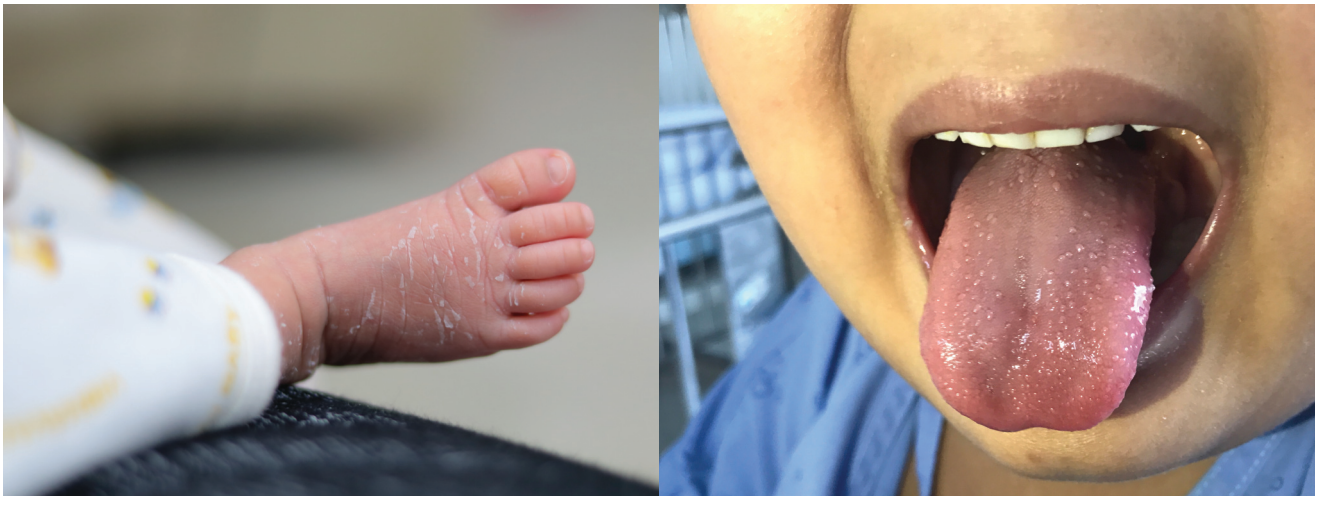
Breastfeeding and vaccinations have been shown to offer protection against the development of Kawasaki disease. Maternal antibodies transferred through breastfeeding and the antibodies produced through vaccination are thought to defend against potential infectious triggers.[9,10]

The incidence of Kawasaki disease in the United States is estimated to be 20 cases per 100,000 children under age 5 years, with rates highest in children of Northeast Asian descent.[11,12] Males have a slightly higher incidence than females. Other risk factors include a family history of Kawasaki disease and polymorphisms in the *CD209* and *ITPKC* genes, which are involved in immune system regulation.[8,13]

PATHOPHYSIOLOGY

Development of Kawasaki disease is thought to be due to dysregulation of the immune system when it encounters microbe-associated molecular patterns. In genetically predisposed patients, the immune system overreacts and initiates a cascade of inflammatory agents, such as tumor necrosis factor alpha (TNF-alpha), interleukins, helper T cells, and cytotoxic T cells. Simultaneously, the response causes downregulation of regulatory T cells and other anti-inflammatory agents. For unknown reasons, in patients with Kawasaki disease this cascade specifically targets the vascular endothelium.[2,6]

FIGURE 2. Desquamating rash (left) and strawberry tongue, two diagnostic criteria for Kawasaki disease



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Three vasculopathic processes characterize the pathophysiology of Kawasaki disease:[14]

- Neutrophil-mediated acute necrosis occurs in all layers of coronary and medium-sized arteries. This process is self-limiting and resolves within 2 weeks of the onset of fever.
- Lymphocytic infiltration of vessel walls results in subsequent inflammation of the vessel. This subacute and chronic vasculitis drives the smooth muscle cells of the middle and outer layers of the vessel wall to transition into myofibroblasts.
- This creates progressive stenotic lesions of the lumen of the vessel, weakening the vessel wall, causing aneurysm and/or stenosis of the artery.[14]

CLINICAL PRESENTATION AND DIAGNOSIS

In the early stages of Kawasaki disease, children are febrile, uncomfortable, and may have a generalized maculopapular rash.[15] Kawasaki disease rarely is on the differential diagnosis list when these children first present, and often they are initially diagnosed with a benign viral syndrome.[15] However, instead of improving as expected, children with Kawasaki disease continue to decline. On examination, they appear ill, inconsolable, and in many cases have conjunctivitis with sparing of the iris (**Figure 1**), erythema of the oral mucosa and tongue ("strawberry tongue"), and cervical lymphadenopathy. In later stages, patients develop desquamation of the fingers and toes (**Figure 2**).[3] The symptoms of Kawasaki disease can be easily recalled using the mnemonic CRASH and Burn (**C**onjunctivitis, **R**ash, **A**denopathy, **S**trawberry tongue, **H**ands and feet, and intermittent high fever for 5 or more days [**Burn**]). Diagnosis of Kawasaki disease is clinical and is made using the criteria listed in **Table 1**.

Some children can present with high fever and fewer than four of the above symptoms, classifying their illness as *incomplete* or *atypical*. Uncommonly, patients may have aseptic meningitis, pericarditis, or hydrops of the gallbladder.[16] The differential diagnosis list for Kawasaki disease is vast and includes adenovirus, enterovirus, streptococcal scarlet fever, measles, Stevens-Johnson syndrome, staphylococcal scalded skin syndrome, juvenile idiopathic arthritis, toxic shock syndrome, Rocky Mountain spotted fever, Epstein-Barr virus, pneumonia, and meningitis.[3]

Laboratory testing and echocardiography can be useful in supporting a diagnosis of Kawasaki disease.[16] Because it is an inflammatory condition, the patient's white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) typically are elevated. If not, other diseases should be considered. No confirmatory laboratory test exists for Kawasaki disease. Within the first 10 days of illness, a pediatric cardiologist should be consulted and an echocardiogram performed to screen for cardiac abnormalities such as coronary artery aneurysm.[17]

TABLE 1. Diagnostic criteria for complete Kawasaki disease[3,24]

Intermittent high fever for 5 or more days plus at least four of the following criteria:

- Generalized maculopapular rash
- Bulbar conjunctival injection with limbic sparing
- Erythema of the lips, throat, and tongue
- Desquamation of the hands and feet
- Cervical lymphadenopathy greater than 1.5 cm

TREATMENT

The mainstays of treatment for Kawasaki disease are IV immunoglobulin (IVIG) and high-dose aspirin. IVIG inhibits inflammatory cytokines, upregulates production of regulatory T cells, and inhibits inflammatory molecules from binding to the vascular endothelium.[2,18] Aspirin is used for its antiplatelet and anti-inflammatory effects.[2] Treatment should be started as early as possible within 10 days of onset of fever.[19] The current US guidelines suggest one dose of IVIG (2 g/kg) and 80 to 100 mg/kg/day of aspirin split and given every 6 hours until the patient is afebrile for 48 to 72 hours.[3] After that time, the aspirin dose should be reduced to 6 to 8 mg/kg once daily until a follow-up echocardiogram is performed 6 weeks after initiation of treatment.[20] If no coronary artery abnormality is present at that time, aspirin treatment may be discontinued.[20]

A rare, but serious complication of high-dose aspirin use in children is Reye syndrome, a potentially fatal illness involving liver failure and acute hepatic encephalopathy.[21] Reye syndrome is associated with influenza or varicella infection.[3] Parents of children who are being treated with aspirin for Kawasaki disease should be advised to seek medical care if their child develops symptoms of influenza or varicella, so that alternative antiplatelet and antipyretic therapies can be initiated.[3]

New adjunctive medications are being researched to further reduce the morbidity and mortality of Kawasaki disease. The HMG-CoA reductase inhibitors of atorvastatin are known to have anti-inflammatory and antioxidant effects that promote healing of the vascular endothelium in adults. Atorvastatin is being investigated in children with acute Kawasaki disease to learn whether the same anti-inflammatory activity can mitigate the disease's destruction of arterial walls.[22]

IVIG RESISTANCE

After it became the standard of treatment in the 1980s, IVIG significantly reduced the morbidity and mortality of Kawasaki disease.[3] However, more than 10% of patients are resistant to IVIG therapy.[23] IVIG resistance is defined as persistence of fever for more than 36 hours after IVIG infusion.[12] Predictive models for scoring patients before

starting treatment can identify those at high risk for resistance. Three widely used Japanese models are the Kobayashi, Egami, and Sano models; however, these scoring systems have low sensitivity for predicting IVIG resistance in patients in North America.[24] Recently, a new score using two ratios, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), have been considered for predicting IVIG resistance. When used together, these ratios have been shown to have equal or higher sensitivity, specificity, and positive predictive value for IVIG resistance compared with the Japanese models.[23]

For patients who have IVIG resistance, alternative treatment is necessary. A second dose of IVIG may be used if the patient has shown some response to the first dose; however, a second dose may have little benefit if the patient did not respond to the first dose.[15] Corticosteroids are used to treat other types of vasculitis and may play an important role for patients who are refractory to IVIG treatment. Corticosteroids should be considered for some patients: those with ongoing fever and other clinical signs greater than 36 hours after receiving the first dose of IVIG, infants under age 1 year, those with persistently elevated CRP after receiving IVIG, and patients who have evolving coronary and/or peripheral aneurysms.[15]

Another emerging treatment for resistant Kawasaki disease uses monoclonal antibody therapy to target TNF-alpha. This proinflammatory agent produced by macrophages plays a key role in the production of inflammatory cytokines, and often is elevated in patients with Kawasaki disease.[25] The level of TNF-alpha elevation has been found to correlate with the development of coronary artery aneurysm.[16] Infliximab, a monoclonal antibody that binds specifically to TNF-alpha, has been shown to reduce duration of fever and to lower CRP levels in patients with IVIG resistance.[16]

COMPLICATIONS

Prompt and appropriate treatment is crucial for patients with Kawasaki disease because of its potentially serious cardiac complications. Coronary artery aneurysm is estimated to occur in about 20% of patients who are not treated or who are treated unsuccessfully.[15] Although 50% to 65% of small coronary artery aneurysms regress within 2 years of treatment, some can cause thrombosis and subsequent arterial occlusion.[26] Patients with coronary artery occlusion must undergo percutaneous stenting of the affected vessel or coronary artery bypass, depending on the severity of the blockage and the number of arteries affected. About 1% of patients with Kawasaki disease will develop giant coronary artery aneurysm, defined as an aneurysm 8 mm or greater in diameter.[26] Giant coronary artery aneurysms rarely regress and nearly always result in stenosis or occlusion. Patients with giant coronary artery aneurysms should be on combined antiplatelet and anticoagulant therapy for at least 3 years after diagnosis, with close follow-up by a pediatric cardiologist.[26] Rarely, children with Kawasaki disease develop myocarditis, pericarditis with pericardial effusion and cardiac tamponade, or Kawasaki disease shock syndrome (hypotension, tachycardia, hepatosplenomegaly, thrombocytopenia, hypoalbuminemia, and hypertriglyceridemia).[27]

FOLLOW-UP

With proper treatment, most children recover without complications.[28] All patients with uncomplicated Kawasaki disease should be followed by a pediatric cardiologist until 6 weeks after treatment was initiated. After this time and when patients display no signs of coronary aneurysm formation, they may be discharged from care. Follow-up for patients with persistent coronary artery aneurysm depends on the size of the aneurysm. For small aneurysms, patients should have an echocardiogram 6 months after diagnosis and then yearly. For large aneurysms, serial echocardiograms should be performed every 3 to 6 months until resolution of the aneurysm and every 1 to 2 years thereafter.[3]

CONCLUSION

Kawasaki disease is an acute febrile systemic vasculitis often seen in young children of Northeast Asian descent. Prompt recognition of the disease and immediate initiation of treatment with IVIG and high-dose aspirin is paramount, as delay could result in long-term cardiac complications. Resistance to IVIG can occur, necessitating the use of corticosteroids or other agents as adjuncts to IVIG therapy. The prognosis for patients with Kawasaki disease generally is excellent with treatment. However, long-term follow-up with a pediatric cardiologist is needed for children who develop persistent coronary artery aneurysms. **JAAPA**

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