Conferences and Reviews

Kawasaki Disease

The Mystery Continues

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Kawasaki disease is an acute systemic vasculitis of unknown cause first described in Japan in 1967. It affects children younger than 10 years, predominantly those younger than 3 years. Children of Asian ancestry are more commonly affected than white children. The diagnosis is made when 4 of the following 5 signs or symptoms are present with fever for at least 5 days: polymorphous rash; conjunctival injection; oral mucosal changes; cervical lymphadenitis; and erythema, swelling, or desquamation of the hands and feet. Various symptoms may be seen also, among them pronounced irritability, arthralgia, and abdominal pain. No diagnostic test exists, and clinicians must carefully exclude diseases that mimic Kawasaki disease. In addition to the above clinical findings, Kawasaki disease causes aneurysm formation in medium-sized arteries, particularly the coronary arteries. Found in about a fourth of patients, these lesions may persist, scar with stenosis, or resolve angiographically. The treatment consists of administering high-dose aspirin and intravenous immune globulin, with the goal of relieving acute illness and minimizing sequelae. Although most respond rapidly, almost 10% of children do not improve clinically with treatment. Complications of Kawasaki disease include myocardial infarction, which may occur during acute illness or later, as a result of coronary abnormalities.

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Since it was first described by the pediatrician Tomisaku Kawasaki almost 30 years ago, the disease that bears his name has been a puzzle for all who have seen and treated it. A multisystem vasculitis of children, Kawasaki disease (also known as Kawasaki syndrome, or mucocutaneous lymph node syndrome) can now be treated effectively in most cases, but its pathogenesis remains unknown. At its worst, it is a condition that damages coronary arteries and may result in fatal myocardial infarction; at its most innocuous, it is an illness of curious mucocutaneous findings and "fever of unknown origin." Because of its potential to cause severe illness, however, physicians who care for children must be able to identify it definitively and treat it promptly.

In 1961, Dr Kawasaki saw his first patient with high fevers, cervical lymphadenopathy, conjunctival and oral mucosal changes, and acral edema. He recounts, "The patient had what we now call typical Kawasaki disease, but looking at him from the perspective of that time, I could not form any clear idea of the disease process involved."[1] Over several years he observed similar cases, sometimes diagnosed by others as "Stevens-Johnson syndrome complicated by carditis." He compiled these in a published series of 50 children in 1967.[2] Initial skepticism regarding the new diagnosis gave way to widespread acceptance with confirmatory reports elsewhere, including an independent discovery of the disease by an American group in the early 1970s.[3]

Epidemiology

It is fitting that Kawasaki disease was described by a Japanese physician; the average annual incidence in Japan is nearly 100 per 100,000 children younger than 5 years, higher than any other major population studied.[4] In North American populations, the incidence for all races combined is about 10 per 100,000 children younger than 5.[5] Asian Americans are at least three times more likely and black Americans two times more likely than whites to be diagnosed with the disease.[6]

Patients with Kawasaki disease are almost always younger than 10 years. The peak incidence is at about 1 year of age and falls off sharply for younger and older age groups. The disease is 1.5 to 2 times more common, and almost 5 times more likely to be fatal, in boys than in girls. Death from Kawasaki disease is a relatively rare event, occurring in less than 0.5% of patients, most of whom are aged 3 years or younger. Death rates appear

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Table 1.—*Diagnostic Criteria of Kawasaki Disease*

Diagnosis is established when fever has been present for ≥5 days, 4 of the following 5 symptoms are present, and other diagnoses have been excluded; if coronary aneurysms are documented, only 3 of the 5 are required

- Erythema, edema, or desquamation of the hands and feet
- Polymorphous rash
- Conjunctival injection (bilateral, non-exudative)
- Lesions of the mouth: Red or cracked lips, strawberry tongue, or injected mucosa
- Cervical lymphadenopathy

inversely proportional to age, with infant mortality approaching 4% in some series.

When a child is diagnosed with Kawasaki disease, his or her siblings have a 2% chance of subsequently becoming ill, suggesting either rare child-to-child spread or occasional shared exposures.[7] Nevertheless, epidemics of the disease have been observed repeatedly in Japan and the United States, occurring every two to three years during the 1980s. About 4% of patients will experience a second case of Kawasaki disease during their childhood. There is a seasonality to its incidence, with a slight increase in winter and spring months.

Etiology

Despite a few areas of encouraging study, the search for the cause of Kawasaki disease has so far been inconclusive. Its similarity to Stevens-Johnson syndrome was appreciated in many early cases, but no association with illness or exposure to medicines was found. The high fevers and the vigorous acute-phase response on laboratory evaluation have made an infectious agent seem likely. Furthermore, the seasonality of the illness, its epidemic nature, and the fact that few children have a second episode of Kawasaki disease suggest infection and acquired immunity. Searches using culture, microscopic examination, and polymerase chain reaction techniques optimized for a plethora of viruses and bacteria have not, however, recovered any single agent consistently.[8–11]

In recent years, researchers have questioned whether a toxin similar to that responsible for the toxic shock syndrome might be the cause of Kawasaki disease.[12] According to this theory, children become ill through colonization with toxin-producing bacteria, until antibodies to the toxin or bacterium are made. This is an interesting hypothesis for several reasons. First, it has been observed that a specific subpopulation of T lymphocytes multiplies rapidly in toxin-mediated diseases such as toxic shock syndrome: those whose T-cell receptors contain $V\beta_2$ variable chains. Some investigators have demonstrated the same marked proliferation in Kawasaki disease,[13] whereas others have refuted this finding.[14] Second, the clinical aspect of the disease, with mucosal changes, rash, and fever, mimics that of toxin-related diseases to the point that it is often confused with them. Finally, the most effective treatment of Kawasaki disease, intravenous immune globulin (IVIG), has been shown to have neutralizing activity against several bacterial toxins.[15] A claim that 69% of patients with Kawasaki disease were colonized with toxin-producing *Staphylococcus aureus*[16] has not been corroborated by other researchers.[17]

Clinical Findings and Diagnosis

The criteria for diagnosis, established in 1971 by a Japanese research committee, are based solely on the clinical findings of the disease (Table 1). Prodromal symptoms are rare. Illness usually begins with high fever of 39°C to 40°C, which may be continuous or spiking in nature. Although the diagnostic criteria used for case reviews include fever for five days, it is not essential to wait five days before making the diagnosis and initiating therapy.

A blotchy exanthem, appearing urticarial, scarlatiniform, morbilliform, erythematous, or any combination of these, appears between days 1 and 5 of the fever (Figure 1). It is seen on extremities and the trunk, with pronounced involvement of the groin in many cases. The rash is not vesicular, although small, aseptic pustules are seen in 5% of patients, particularly on the knees.

Palms and soles do not show discrete lesions, but are deeply erythematous and often become tensely edematous also. At about day 10 of the illness, they desquamate. Starting at the fingernails, sheets of palmar skin peel off, followed a few days afterward by the plantar skin in a similar manner.

Two to four days after the onset of fever, the bulbar conjunctivae become injected. This may be subtle or pronounced and may be accompanied by the finding of anterior uveitis on slit-lamp examination. There is no conjunctival exudate. Bright red lips with cracking and bleeding, along with a strawberry tongue, reminiscent of group A streptococcal disease, appear at about day 3 to 5. Erythema of the oral mucosa may also be seen.

Adenitis, occasionally appreciable before the onset of fever, develops in two thirds of patients. It can be profound, bilateral or solitary, and painful to the child, but it is never suppurative. Usually cervical in location, it is the least frequently observed of the diagnostic criteria for Kawasaki disease. Because this may be the only prominent finding initially, the disease may at first be indistinguishable from bacterial adenitis.[18]

In addition to the diagnostic criteria, numerous other findings are associated with Kawasaki disease (Table 2). Ten percent of children with the disease have right upper quadrant abdominal pain related to hydrops of the gallbladder, and the total serum bilirubin level is often slightly elevated. Diarrhea with or without vomiting is seen in a third of patients with the disease. Joint pains due to aseptic arthritis are seen in a similar fraction. Large and small joints are affected, frequently with substantial effusion. Aseptic meningitis is diagnosed in about a fourth of patients. Marked irritability is noted in

Table 2.—*Findings Associated with Kawasaki Disease*

System	*Signs or Symptoms*
CNS	Meningismus, irritability, sensorineural hearing loss, CSF pleocytosis
Ophthalmologic	Anterior uveitis
Cardiovascular	Tachycardia, gallop rhythm, myocarditis, pericardial effusion, aortic insufficiency, mitral insufficiency, conduction abnormalities, coronary artery ectasia, myocardial infarction
Gastrointestinal	Vomiting, diarrhea, pancreatitis, gallbladder hydrops, hyperbilirubinemia
Renal/Urologic	Sterile pyuria, microscopic hematuria, albuminuria
Hematologic	Hypercoagulable state (thrombocytosis with platelet activation), peripheral gangrene
Musculoskeletal	Arthritis, neck pain

CSF = cerebrospinal fluid

infants, even when the cerebrospinal fluid is normal. Sinus tachycardia at rest is seen in most patients. An ophthalmologic evaluation may be helpful in differentiating Kawasaki disease from other illnesses; anterior uveitis is found on slit-lamp examination in most patients,[19] distinct from the findings in adenoviral conjunctivitis or of the Stevens-Johnson syndrome.

The course of Kawasaki disease generally has three phases. The acute phase is the initial approximately ten-day period of fever, oral changes, acral edema, injection of the conjunctivae, and lymphadenitis. Next, the subacute phase is the period when fever and skin findings have resolved, but irritability and conjunctival injection may continue. Desquamation of hands and feet occurs during this phase, which lasts from about day 10 to day 24. The third, or convalescent phase, begins on the resolution of the clinical signs and ends when blood test results return to normal, as discussed later.

Diagnostic Confusion

Although the diagnostic criteria are well defined and familiar to many physicians, KD is frequently confused with other conditions. There are a few reasons for this: First, infants are notorious for presenting atypically, with the diagnostic features appearing only after several days of illness. Second, signs required for the diagnosis are not specific; several "look-alike" conditions must be excluded (Table 3). Finally, KD is associated with a diverse array of findings. A single symptom or sign may, in any one child, appear to be the predominant focus of illness, and lead to misdiagnosis.

The following is such a scenario: A 9-month old infant is brought to her pediatrician because of fever. There are no impressive physical findings, but her white blood cell count is high, and a urinalysis shows white blood cells. The child is treated with antibiotics for presumed urinary tract infection. The next day, conjunctivitis and rash appear, and are construed as a reaction to the antibiotics, which are then changed. Only when cultures are negative and the case is fully reevaluated does KD enter the differential diagnosis. Similarly, joint pains due to KD have been treated as septic arthritis, and abdominal pains as hepatitis. A raised level of suspicion is the most important factor in making a prompt diagnosis.

Laboratory and Other Data

The characteristic laboratory findings of Kawasaki disease reflect an exuberant acute-phase response but are not unique to the disease. A complete blood count often shows an elevated leukocyte count with a leftward shift. The erythrocyte sedimentation rate and C-reactive protein level are greatly elevated, as are platelet counts, which frequently exceed $1{,}000 \times 10^9$ per liter (1 million per mm^3) in the subacute phase. The erythrocyte sedimentation rate declines with a response to treatment and the resolution of illness.[20] A total serum bilirubin level may be elevated, but rarely exceeds 86 μmol per liter (5 mg per dl). Mild hypoalbuminemia is consistently recognized, for unclear reasons. Sterile pyuria and albuminuria due to urethritis are seen early in the illness. Similarly, cerebrospinal fluid analysis reveals monocyte-predominant pleocytosis and is sterile.[21]

Electrocardiographic abnormalities are common but subtle. They include mild PR interval prolongation, T-wave flattening or inversion, and nonspecific ST segment changes. Persistent findings on serial electrocardiograms are predictive of coronary artery lesions.[22] Echocardiography during the acute phase may reveal pericardial effusion, which rarely becomes clinically important. Coronary artery ectasia, or regional dilation, may also be seen.

Pathologic Findings

Kawasaki disease is a systemic arteritis, with particular involvement of the coronary arteries. Intense infiltration of vessel walls with inflammatory cells is seen on biopsy specimens of various tissues from acutely ill children. Involvement of the intimal layer is seen during the

Table 3.—*Look-alike Conditions Frequently Confused With Kawasaki Disease (KD)*

Condition	*Features Distinguishing the Condition from KD*
Adenovirus	Rhinitis, pharyngitis often exudative, or punctate keratoconjunctivitis on slit-lamp examination
Bacterial adenitis	Fluctuance of node, no conjunctival injection, no cracked lips, no rash, or culture-positive node aspirate
Measles	Discrete lesions on palms and soles, exudative conjunctivitis, cough, rhinorrhea, upper respiratory tract symptoms preceding rash
Scarlet fever	Exudative pharyngitis, more common in school-aged children (rare <2 years), positive culture for group A streptococcus, or elevated anti-streptolysin O titer
Stevens-Johnson Syndrome	Infectious or pharmacologic cause, flaccid bullae, Nikolsky sign, or sloughing of palpebral conjunctivae
Toxic shock syndrome	Diffuse erythroderma (sunburn-like), thrombocytopenia, hypotension, or focus of staphylococcal infection
Urinary tract infection	Urine culture positive for pathogens, no skin findings, or urine test positive for nitrites

acute phase of illness, with panvasculitis and aneurysm formation usually in the subacute phase.[23] The coronary arteries are most commonly affected, but aneurysms have been located in other medium-sized arteries such as the brachial, internal iliac, and intercostal arteries. Aneurysms may be saccular or fusiform and may either persist or heal, occasionally with scarring and stenosis. The involvement of vessels occasionally leads to acute thrombosis, with ischemic injury. Its predilection for the coronary circulation has made this disease the leading cause of acquired heart disease in children of developed countries.

In addition to coronary vessel involvement, Kawasaki disease may affect other areas of the heart. Carditis with variable impairment of cardiac function, pericarditis with effusion, mitral and aortic valvulitis, and conduction system inflammation have been observed.

Workup and Treatment

When clinical features suggest the diagnosis of Kawasaki disease, laboratory values support it, and other diagnoses are reasonably excluded, patients are generally admitted to a hospital for observation and treatment. When available, a pediatric cardiologist should be consulted to obtain a baseline echocardiogram, to assist in the management of any cardiac insufficiency, and to arrange for follow-up care. It may be desirable to freeze an acute serum specimen because the IVIG treatment will alter titers if they are to be measured later.

Aspirin

Aspirin is used in the treatment of Kawasaki disease because of its anti-inflammatory and antiplatelet functions. A high dose (100 mg per kg of body weight a day orally, divided, every 6 hours) has been shown to be safe and effective in reducing fever and clinical illness.[24] The duration of high-dose aspirin treatment varies, but most experts continue it through day 10 to 14 of the illness and until the patient has been afebrile for 48 to 72 hours. The dose is then reduced (to 3 to 5 mg per kg a day as a single dose). Aspirin can be discontinued when acute-phase reactants such as the erythrocyte sedimentation rate return to normal four to six weeks later.

A serum salicylate level should be measured if signs of toxicity such as nausea, lethargy, or hyperpnea develop. A different antiplatelet agent should be used if the diagnosis of influenza or varicella is made concurrently, due to the theoretical risk of Reye syndrome.

Intravenous Immune Globulin

The benefit of IVIG in reducing the manifestations and complications of Kawasaki disease has been shown by several investigators. It was shown in a prospective multicenter trial to reduce the incidence of coronary aneurysms from 17% to 4%, but the mechanism of this effect is still not known.[25] Pooled from the plasma of more than 1,000 blood donors, several commercial preparations are available. Various dosing regimens have been used in different centers, but recent data support the use of a single dose of 2 grams per kilogram, infused over 10 to 12 hours.[26]

In many patients, the clinical response to the infusion of IVIG is striking, with the abatement of fever and improved laboratory indices within 24 hours. Side effects are unusual but include fever, chills, hypotension, and rarely, hemolytic anemia with disseminated intravascular coagulation.[27] Patients should, therefore, be monitored closely, with vital signs checked hourly throughout the infusion.

Treatment Failure

In all major series, there is a group of patients, making up 8% to 10% of the total, whose illness does not respond to IVIG in the expected way. Children in whom fever persists through treatment or returns two to four days thereafter should be carefully reassessed for alternative diagnoses. If Kawasaki disease is still suspected, they can be safely re-treated with a second infusion of IVIG.[28] Most patients respond to the second infusion, but some do not. Of note, patients requiring IVIG retreatment appear to have a higher rate of coronary aneurysms than those responding to a single infusion, regardless of their response to the second treatment (M.P.G. and J. C. Burns, MD, written communication, October 1997). In one center, pulsed doses of corticosteroids were administered to four children who had persistent or recrudescent fever after repeated IVIG

Figure 1.—Physical findings in Kawasaki disease (KD) are illustrated. A 4-year old boy with Kawasaki disease (A) demonstrates the red, cracked lips typical of the illness. His conjunctivae are injected, and a right subconjunctival hemorrhage is present. Injection of the conjunctivae (B) is without exudate and is less pronounced immediately around the limbus. The exanthem of KD may take many forms but is frequently blotchy, pink, and maculopapular (C).

infusions. Coronary aneurysms did not develop in any of the four.[29]

The xanthine derivative pentoxifylline may be of benefit in preventing aneurysms, particularly in cases of IVIG failure. Traditionally used to decrease blood viscosity in patients with claudication, pentoxifylline blocks the production of tumor necrosis factor α, which is thought to be an important inflammatory mediator in Kawasaki disease. In a recent Japanese trial of Kawasaki disease, aneurysms developed in 3 of 21 patients treated with IVIG. None of the 20 children treated with high-dose pentoxifylline and IVIG had aneurysms.[30]

All treatments for Kawasaki disease other than IVIG and aspirin are at this time considered investigational.

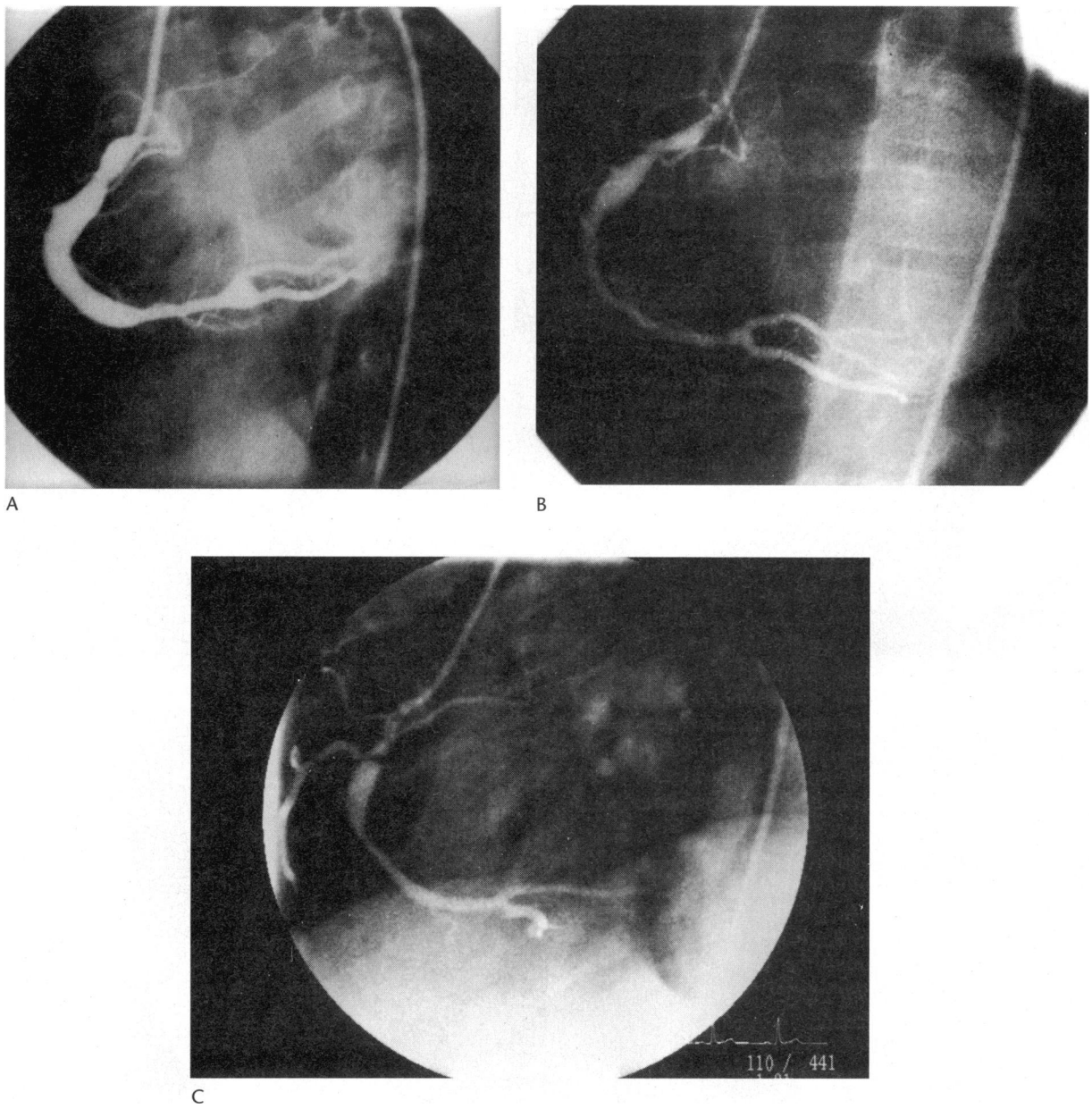

Figure 2.—Serial right coronary angiograms in a patient with sequelae of Kawasaki disease are shown. Three months after acute illness (A), this patient had a large aneurysm of the proximal two thirds of the right coronary artery. Two years later (B), it had regressed. Another angiogram 16 years after the illness (C) shows high-grade stenosis. This patient had involvement of the left coronary artery also, with persistently abnormal stress thallium tests. (Photographs courtesy of James W. Wiggins, MD.)

The management of cases refractory to standard treatment should be undertaken only with the assistance of a specialist experienced with such cases.

Complications

The best-known complication of Kawasaki disease and that thought to have the most serious long-term consequences is coronary aneurysm formation. Treatment with IVIG substantially reduces the incidence of this sequela (seen in a fourth of untreated patients), but has not eliminated it. Ectasia, frequently recognized on echocardiograms in the acute phase of the illness, often resolves. Aneurysms usually appear in the subacute phase, but have been seen as early as five days after the onset of fever. More than half of aneurysms that form during the course of Kawasaki disease will regress considerably over the months that follow acute illness.[31] Some heal with stenosis and notable obstruction to blood flow (Figure 2). Even when coronary angiograms return to normal, however, there is evidence that functional properties of the vessel remain impaired.[32]

When an aneurysm or aneurysms have been identified, aspirin treatment may be continued for months and follow-up continued with serial echocardiography. Warfarin sodium may be added when highly obstructive lesions have been identified on angiography. Stress testing is often done to look for ischemic changes when abnormalities of the coronary arteries persist.

Probably the most serious complication of Kawasaki disease, myocardial infarction, occurs in less than 0.5% of patients. Manifested by shock and vomiting clinically, myocardial infarction is found at autopsy in most fatal cases.[33] Death due to Kawasaki disease usually occurs in the subacute phase.

It remains to be determined what contribution, if any, Kawasaki disease makes to ischemic heart disease in adults. In a recent follow-up study, children did not appear to have increased mortality after their acute illness,[34] but late sequelae have been reported,[35] and longer-term follow-up may be required to define their contribution to adult heart disease.

Other reported cardiac lesions are acute and chronic insufficiency of the aortic and mitral valves presumably from inflammatory damage, myocardial dysfunction with heart failure, conduction system inflammation, and myocardial fibrosis. Ischemic injury resulting in gangrene of the extremities has been reported as a complication of the disease in infants.[36] This rare situation has been treated successfully with the infusion of prostaglandin E_1.[37]

Conclusion

Great advances have been made in the characterization and treatment of Kawasaki disease. A disorder first described only 30 years ago, it is now recognized in all races around the world. Nonetheless, a great deal remains to be determined about this mysterious disease. Two developments are urgently needed: a definitive diagnostic test for the disease, and a treatment for cases refractory to the current standard of care, aspirin and IVIG. Although promising leads are being followed in many laboratories already, the search for improved diagnosis and treatment will be simplified when the pathogenesis of the disease is finally understood.

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