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Kawasaki Syndrome: An Update

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Fifteen years' experience with this "new" multisystem disease of very young children has led to a broader understanding of its clinical behavior, pathology, epidemiology, and spectrum of associated cardiovascular complications, including fatal myocardial infarction. Long-term follow-up of a large number of survivors has yielded unexpected findings of significant residual sequelae.

Experience with Kawasaki syndrome is now in its adolescence, as are many of the patients who survived their bouts with the syndrome since it was first recognized and described in Japan 15 years ago. As is true of adolescence in any context, we have learned a good deal, and we still have a good deal to learn—in this case about the entity termed mucocutaneous lymph node syndrome (MCLS, MLNS) by Tomisaku Kawasaki when he reported his first 50 cases in 1967.

Our experience in Hawaii has closely paralleled that of the Tokyo pediatrician, although we were unaware of his findings until they were published in English in 1974. By that time, we had independently identified the same diagnostic criteria for the disease in a dozen cases dating back to 1971.

Since that time, both the clinical and epidemiologic experience with the disease have broadened considerably (see D. M. Morens and A. J. Nahmias, "Kawasaki Disease: A 'New' Pediatric Enigma," HP, September 1978). While early clinical attention was understandably focused on early recognition, acute management, and efforts to determine the etiology, it became obvious by the early 1970s that a small percentage (1% to 2%) of patients died of acute coronary artery thrombosis at a time when they were thought to be convalescing. We now have significant long-term follow-up of a group of patients demonstrating residual cardiovascular sequelae in those who survived.

Although characterization of the syndrome is only 15 years old, we have no reason to believe that it is a new disease. We have found a report of a case with compatible autopsy findings in 1887 in an American Caucasian child. In the past the illness may have masqueraded in various guises. Old descriptions of infantile polyarteritis nodosa are pathologically identical to fatal Kawasaki syndrome. Many cases may have been diagnosed as "unusual" measles. Another possibility that cannot be excluded [illegible] considering where Kawasaki syndrome may have been "hiding" is rheumatic fever. There are certainly enough resemblances, with respect to both acute phase manifestations and sequelae, to make it conceivable that in the days when rheumatic fever was prevalent, Kawasaki syndrome was misdiagnosed, perhaps as a somewhat atypical rheumatic fever or as rheumatic heart disease.

Epidemiology

The syndrome originally was widely considered to be a rare curiosity occurring in the Orient, but the broader epidemiologic picture that has emerged in recent years is intriguing. Kawasaki syndrome has been recognized worldwide in children of all racial groups. However, it is markedly more prevalent in Japan and in Japanese children in Hawaii—not in Orientals lumped together, but specifically in those of Japanese ancestry. In Hawaii, these patients are usually fourth-generation Americans, completely assimilated. We have encountered epidemic as well as endemic incidence of the illness with no clear evidence of person-to-person spread or unique environmental associations.

The Japanese have surveyed more than 24,000 Kawasaki patients and have not found any clear geographic or urban-rural differences in the incidence of the disease in children under four. No links to diet, general health, or environment could be identified, and no clear seasonal pattern was seen. Nor is there any evidence for either person-to-person transmission or common-source exposure.

The disease is currently more prevalent among Japa-

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nese children in Hawaii than it is in Japan, with a yearly incidence of more than 20 cases per 100,000 children. Japanese children comprise almost 70% of our total of more than 200 Kawasaki cases. In Hawaii, as elsewhere, cases are encountered in children of diverse racial and ethnic groups. Caucasian children appear to be specifically *underrepresented*, with mixed race, Polynesian, Korean, Chinese, Filipino, and black children distributed normally. The U.S. cases reported to the Centers for Disease Control indicate that prevalence is highest among Orientals, intermediate for blacks, and low for Caucasians.

Sporadic cases and temporally limited community-wide epidemic outbreaks have been reported in Caucasian and mixed populations in widely distant parts of the United States (New York City, eastern Massachusetts, Philadelphia, Newark, and Los Angeles). In recent outbreaks in Boston and Rochester, N.Y., the incidence of Kawasaki syndrome rose from one and four per 100,000, respectively, to more than 150 per 100,000 in a three- to four-month period.

Because the disease appears to be most prevalent in Japan and among Japanese children in Hawaii, a unique genetic susceptibility is suspected. No single HLA antigen has been found to be common among all cases, and no systematic study has examined the prevalence of any other genetic marker for the disease.

Kawasaki syndrome no longer appears to be rare. We feel that the rise in cases now encountered cannot be attributed entirely to increased recognition. We have been maintaining an active surveillance system for this syndrome since 1973, with the number of cases showing a steady increase.

Kawasaki syndrome is, overwhelmingly, an illness of young children: 50% of the victims are less than two years old, while 80% are under four. The disease rarely affects anyone older than eight, and the literature contains only two confirmed cases of adult Kawasaki syndrome. (The majority of cases reported as "adult Kawasaki syndrome" now appear to be examples of another, newly discovered disease, toxic shock syndrome.) Males are predominantly affected, at a ratio of 1.5:1.

Clinical Features

Kawasaki syndrome progresses through a series of predictable phases. A positive diagnosis can be made only when a patient fulfills five of the six clinical criteria (see table on page 102). There is some variation in the severity of these symptoms, but their type and timing are remarkably constant. Over 90% of Kawasaki patients exhibit all of the first five criteria; the sixth, lymph node enlargement, is seen in only about half of them.

Diagnosis must be made by strict adherence to these criteria together with exclusion of diseases that could mimic Kawasaki syndrome. Physicians who diagnose a case that omits two of the six criteria may, for example, misdiagnose an allergic reaction as Kawasaki. Failure to exclude treatable bacterial disease may have tragic consequences. We know of one case in which a child presumed to have Kawasaki syndrome died of streptococcal scarlet fever and sep

Other illnesses that may mim Kawasaki include measles, leptospirosis, streptococcal scarlet fever, staphylococcal "scalded skin" syndrome, Yersinia enterocolitis, exanthematous rickettsial disease (especially Rocky Mountain spotted fever), rubeola, enteroviral illnesses, and certain illnesses in the collagen-vascular disease group, including juvenile rheumatoid arthritis, lupus erythematosus, and Reiter's syndrome. Many of these diseases can be ruled out because they usually do not exhibit all of the manifestations of Kawasaki syndrome. It is essential for diagnostic certainty that the appropriate cultures and investigations be done. There are no consistent or pathognomonic laboratory tests by which Kawasaki syndrome can be identified.

The course of the disease can best be described as triphasic. An acute early phase is characterized by fever, conjunctival injection, changes in the lips and mouth, swelling of hands and feet, erythematous rash, and lymph node enlargement. As the rash, fever, and lymphadenopathy subside, usually by about the tenth day following the fever's onset, a subacute phase begins. This period is the most dangerous because this is when the arthritic manifestations, cardiac disease, and platelet elevation occur—and when the risk of death is highest. When all signs of illness fade, after about 25 days, a convalescent phase begins that lasts until the sedimentation rate returns to normal.

About 2% of Kawasaki syndrome patients die, usually of massive myocardial infarction that results from acute thrombosis of aneurysmally dilated coronary arteries. Seventy percent of the deaths occur 15 to 45 days after the onset of fever. This period, according to pathologic data, is characterized by well-established coronary vasculitis. As this coincides with the period of universal presence of an elevated platelet count, the patients are in jeopardy of coronary thrombosis. In most children Kawasaki syndrome is self-limited. The prognosis in

Kawasaki Syndrome Outbreaks

Winter 1978	40 cases	New York City
Winter–Spring 1978	30 cases	Honolulu
Winter 1979	23 cases	Rochester, N.Y.
Spring 1980	57 cases	Boston
Winter–Spring 1980	20 cases	Los Angeles
Winter–Spring 1981	63 cases	Honolulu

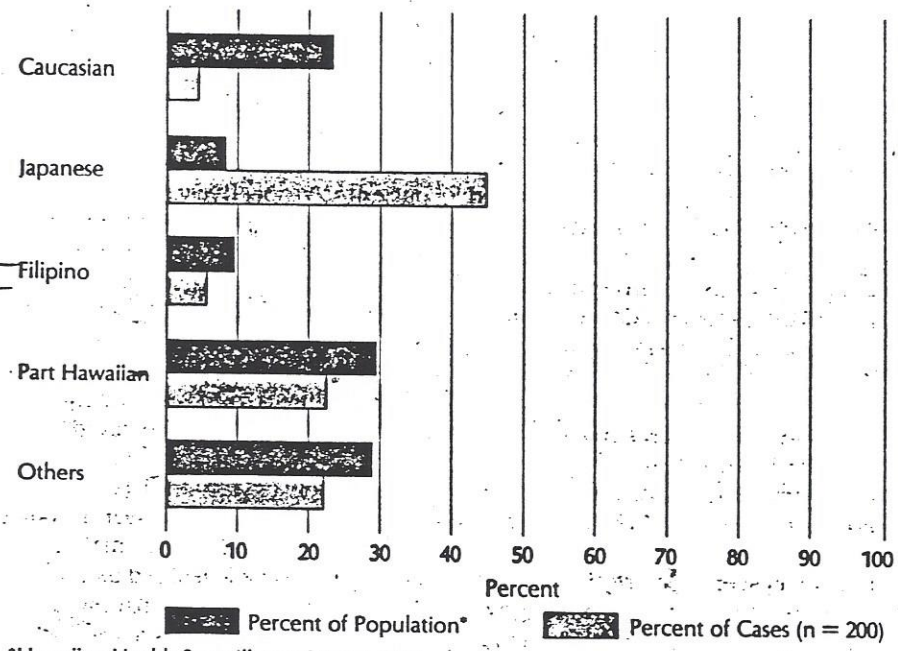
each case depends on the extent and severity of cardiovascular damage.

During the initial, acute phase, patients are usually severely ill. Their fever begins abruptly and can spike to ≥40° C (104° F) several times a day, dipping only to ≥37.8° C (100° F). Fever persists for five to 23 days, with an average duration of 11 days.

Within two days of the fever's onset, conjunctival injection usually appears. It is a discrete injection of the blood vessels of the bulbar conjunctiva without generalized suffusion. This persists throughout the febrile period and may last as long as three to five weeks. One group has also reported seeing very mild anterior uveitis. The conjunctivitis of Kawasaki syndrome is typically not purulent, and corneal ulcers do not occur, distinguishing it from the conjunctivitis of Stevens-Johnson syndrome.

Facial changes include some swelling, pallor, erythema of the lips and the oropharynx, and hypertrophic papillae of the tongue (giving it a "strawberry" appearance). These symptoms appear simultaneously within one to three days after the onset of fever. In most patients, the lips will crack, fissure, and bleed by the sixth to seventh day. Ulcers inside the mouth are rare and the oropharynx erythema is not accompanied by pain, but the children frequently complain of lip soreness. The strawberry tongue resembles that seen in streptococcal scarlet fever or toxic shock syndrome.

Changes in the hands and feet are the most distinctive feature of Kawasaki syndrome. Within three days of the onset of fever, a generalized purple-red discoloration appears on the palms and soles, along with a firm, indurative edema of the hands and feet. The skin is tightly stretched over these indurated tissues, which are wood-hard, unlike the soft, boggy pitting edema seen in toxic shock syndrome. The swollen areas become so hard that they cannot be dented by pressure, and the fingers display a fusiform swelling. The condition resembles acute scleroderma and persists for five to seven days. When the swelling appears in a subtle form, it is minimal, but the child refuses to walk and is clumsy with his hands. He cannot use scissors or crayons or pick up objects.



The disproportionate incidence of Kawasaki syndrome in children of Japanese ancestry and its underrepresentation in Caucasian children is indicated by these data, which were drawn from a sample of 200,000 Hawaiians and 200 children with the syndrome. Other racial and ethnic groups appear to distribute proportionally.

Between the tenth and fourteenth days, the skin on the hands begins to peel, starting under the fingernails. This desquamation begins in the feet a few days later and spreads, involving the entire palms and soles. The skin comes off in a large cast, not in flakes, and there is normal skin underneath. Peeling in other parts of the body, such as knees and elbows, is seen in only 10% of cases. During the convalescent phase, deep transverse grooves appear across each fingernail and toenail, gradually growing out with the nail. This could be caused by a brief arrest in the maturation of the cells in these areas as a result of the fever.

Nearly all patients exhibit a deeply erythematous exanthem, which occurs concurrently with or soon after the onset of fever. It can take many forms, the most common of which is a pruritic, urticarialike exanthem with large, irregularly shaped, raised erythematous plaques. The rash is widespread on both the trunk and extremities but is frequently most severe in the perineal region. Another common form is a deeply erythematous maculopapular eruption, similar to that of measles. About 5% of Kawasaki patients have a rash that looks like erythema marginatum, such as that seen in rheumatic fever, while in less than 5%, the rash resembles the flush of scarlet fever. This distinguishes Kawasaki syndrome from toxic shock syndrome as well as from streptococcal scarlet fever, both of which primarily display a scarlatiniform rash.

A small number of children (about 10%) develop a sterile, vesiculopustular eruption, usually on knees and elbows (miliaria pustulosa). Sometimes the vesicles are empty, while at other times they contain a small amount of white material that includes leukocytes. This change appears at about the eighth day and resolves within several days.

Lymph node enlargement is, as we have said, the least common criterion of Kawasaki syndrome. It usually occurs on one side of the neck, with a single, firm, enlarged node measuring 1.5 cm in diameter. The enlarged node is often red and indurated, but rarely warm, and does not suppurate. It normally appears within three days after the onset of fever, lasting through the febrile period and up to a week beyond, although we have seen some patients in whom it has persisted for more than three weeks.

Other features frequently seen in the course of Kawasaki syndrome attest to its multisystem involvement. Urethritis, accompanied by pyuria, is seen in more than 75% of the patients. A smaller number also show transient, microscopic hematuria. These symptoms do not appear to be due to renal involvement but rather seem to originate in the urethra. Indeed, renal involvement is so unusual that, if encountered, it should prompt a serious reconsideration of the diagnosis.

Kawasaki Syndrome
Principal Diagnostic Criteria

- Fever, for more than five days
- Conjunctival injection
- Changes in the mouth
  - Erythema, fissuring, and crusting of lips
  - Diffuse oropharyngeal erythema
  - Strawberry tongue
- Changes in the peripheral extremities
  - Induration of hands and feet
  - Erythema of palms and soles
  - Desquamation of tips of fingers and toes approximately two weeks from onset of illness
- Transverse grooves across fingernails two to three months after onset of illness
- Erythematous rash
- Enlarged lymph node mass >1.5 cm in diameter

Associated Manifestations

- Pyuria
- Arthralgia, arthritis
- Diarrhea
- Abdominal pain
- Aseptic meningitis
- Carditis
- Hepatitis
- Obstructive jaundice
- Hydrops of gallbladder

Arthritis and arthralgias are observed in about 35% and 45% of patients, respectively. They occur late in the acute or during the subacute phase, with a mean time of onset at day 10. Large joints in the lower extremities (hips, knees, and ankles) are affected most often, but joints in the upper extremities (wrists, elbows, and small joints in the hands) can also be involved.

We have analyzed the fluid from affected joints and find that it is very similar to the type seen in patients with rheumatoid arthritis. The fluid can be classified as group II inflammatory fluid, with low viscosity. The cell count in the fluid ranges from 20,000 to 200,000/cc and consists primarily of polymorphonuclear cells. We have never been able to isolate any organism from the fluid.

The arthritis usually lasts eight to 10 days, but we have seen it persist in one case as long as five months. Chronic arthritis, however, does not appear to result.

Central nervous system effects are seen to some degree in nearly all Kawasaki patients. They often take the form of a pronounced irritability, frequent mood changes, and disturbed sleep. About 25% of patients have aseptic meningitis with severe lethargy, stiff neck, and a white blood cell count of 25 to 100/mm^3 in the cerebrospinal fluid. CSF pleocytosis is primarily lymphocytic. In extreme cases, a child may sink into a semicoma or coma for one to several days.

A quarter of the Kawasaki patients also show gastrointestinal distress, consisting of diarrhea and abdominal pain. About 10% suffer hepatitis during the acute phase. A very distinctive and unusual complication (affecting approximately 5%) in the first or second week of illness is an accumulation of clear, watery fluid in the gallbladder (acute hydrops of the gallbladder). The material in the bladder is not very bilious, and jaundice will accompany this condition only occasionally. This is suspected when a right upper quadrant mass is palpated and can be confirmed and followed by ultrasound examinations. As the patient improves, after about four weeks, the gallbladder returns to normal size.

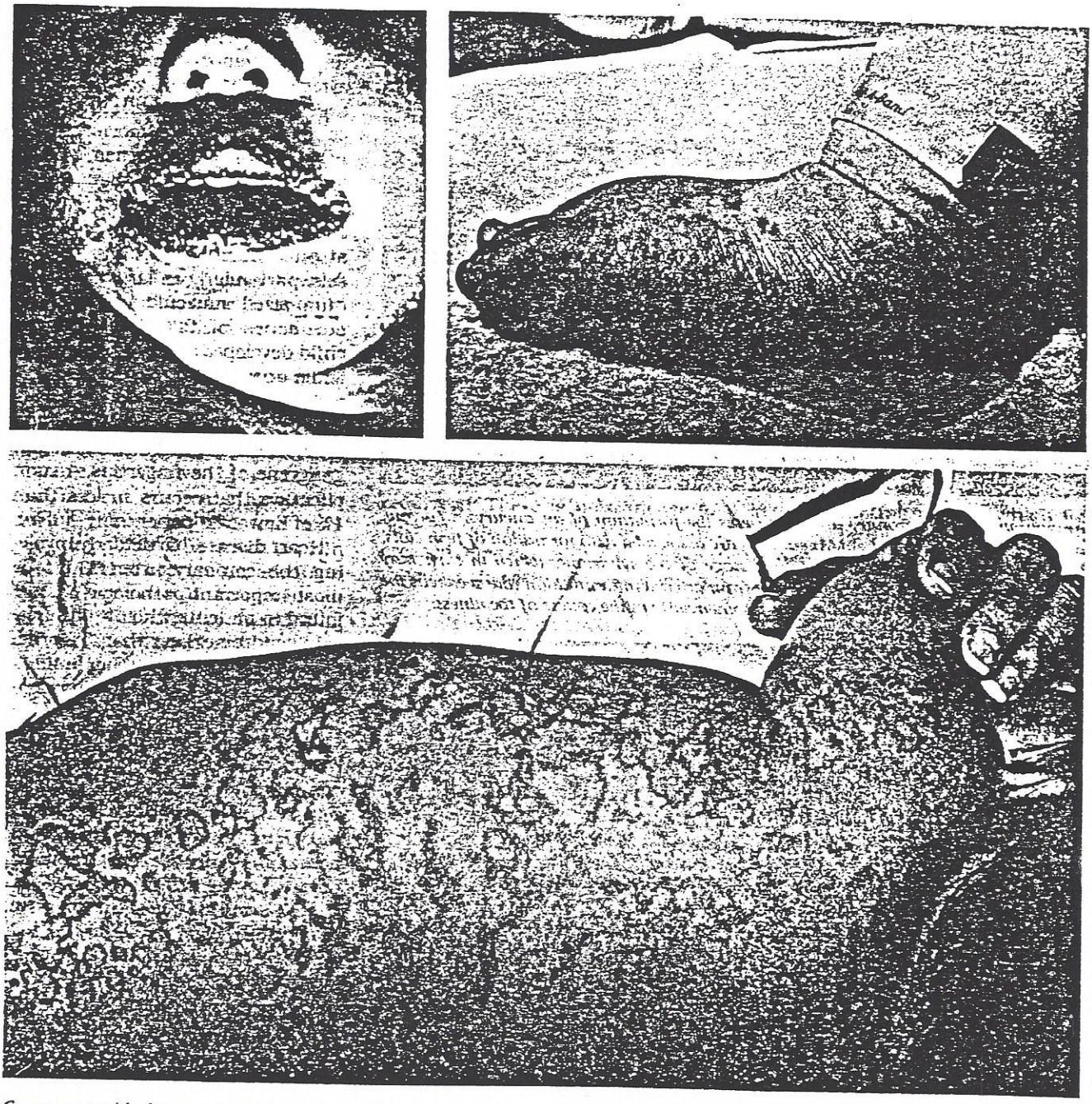
Laboratory abnormalities associated with Kawasaki syndrome are too variable or appear too late to be diagnostic. Total white blood cell counts rise during the acute phase. Counts of greater than 20,000 mm/^{3} are seen in over half the patients, while counts of greater than 30,000 are not uncommon. Polymorphonuclear leukocytes predominate. The erythrocyte sedimentation rate and C-reactive protein in the serum uniformly rise during the acute phase and then gradually subside, usually reaching normal values by six to 10 weeks after the onset of illness.

Thrombocytosis is universal in Kawasaki syndrome, but platelet values usually remain normal during the acute phase. They begin to increase after about the tenth day of illness, peaking at 600,000 to 1.8 million between days 15 and 25 of the disease, and then return to normal by day 30.

All of the immunoglobulins (IgM, A, G, and E) may show an acute rise during the illness and then fall. SGOT, SGPT, and bilirubin show modest elevations in the minority of patients who develop hepatitis.

Cardiac Involvement

Clinical cardiac disease, due to vascular and cardiac inflammation, occurs in at least 20% of Kawasaki patients. During the acute phase, severe tachycardia and gallop rhythm are most common, but the more serious abnormalities (congestive heart failure, pericardial effusion, serious arrhythmias, and mitral insufficiency) generally appear during the subacute stage. These more serious abnormalities are usually manifestations of acute carditis and tend to appear between the ninth and twenty-first days after onset of fever. Congestive heart failure may be treated by cautious digi-

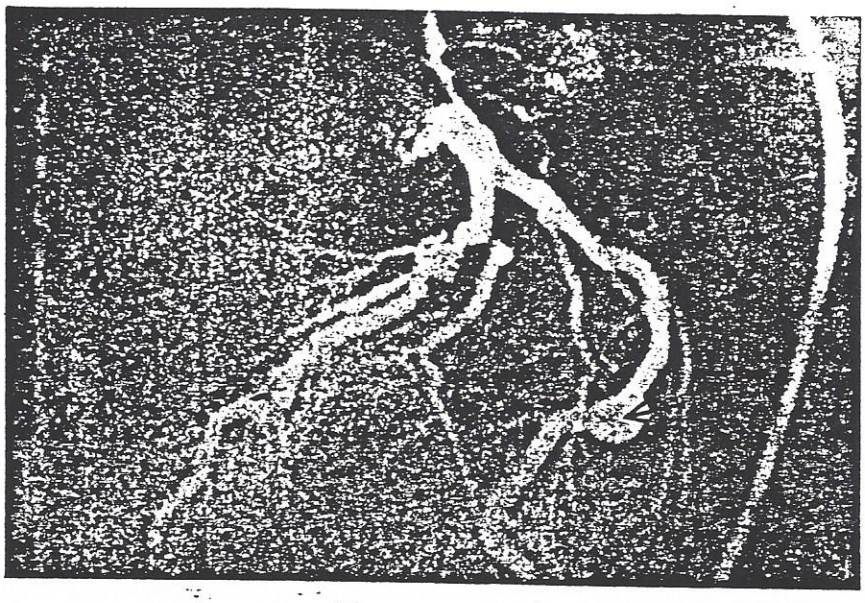


Concurrent with the onset of Kawasaki come characteristic facial changes that include (top, left) red, cracked lips, swelling, and a pallor surrounding the mouth. Early signs also include reddening and swelling of the feet (top, right), so that they become firm and indurative, and a deeply erythematous exanthem (bottom) that is widespread on the trunk and extremeties.

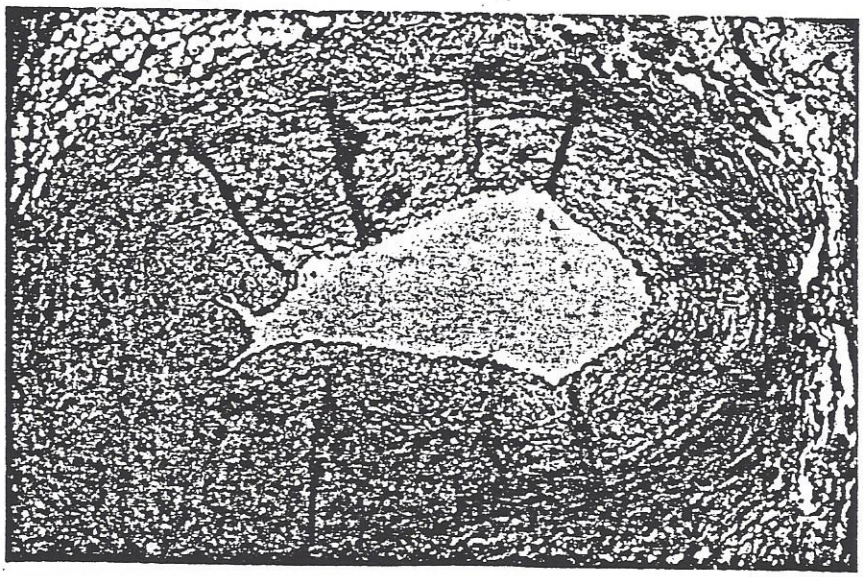
talization. The duration of carditis generally varies from one week to over one month. Mitral insufficiency may persist for several months.

Coronary artery aneurysms may also be diagnosed during life by coronary angiography or by two-dimensional echocardiography. Selective coronary artery angiography is the most sensitive method, but it requires catheterization, an invasive procedure that cannot be tolerated by all of these young patients. Two-dimensional echocardiography is almost as sensitive in detecting coronary artery aneurysms and should be used in screening all Kawasaki patients during the subacute stage (after day 28) of illness. Electrocardiography is not a sensitive tool for detecting or managing cardiac complications of Kawasaki syndrome. When we examine ECGs, it appears that about 30% of the children have some cardiac abnormality, primarily heart block, arrhythmias, and voltage changes suggesting left ventricular hypertrophy.

Using two-dimensional echocar-



Angiograph of the coronary arteries reveals the formation of an aneurysm (arrow, above) in a Kawasaki patient. Aneurysms are associated with formation of firm clots, particularly during the thrombocytotic stage of the syndrome, which in turn may cause fatal infarction. Aneurysms result from arterial inflammation that weakens the vessel's internal, elastic lamina (below), shown early in the course of the illness.



diography, we have found aneurysmal dilations in 17% of 118 unselected Kawasaki patients during the fourth week of illness. Three Japanese series have detected aneurysms in 14% to 20% of unselected patients during the same period.

It now appears likely that a spectrum of coronary vessel involvement, ranging from minor, asymptomatic inflammation to fatal infarction, occurs in *all* Kawasaki patients. Fatalities are not limited to patients with clinical signs of cardiac disease but have also been associated with inflamed and weakened blood vessels in children without such clinical signs.

Aneurysms have a tendency to regress within one year. The only good study to examine this evolution showed that one half to two thirds of the children who had aneurysms detected by angiography in the fourth and fifth weeks of illness did not have the lesions a year later. The remainder exhi either persistent aneurysms o narrowed and tortuous coronar arteries. It is likely, however, tha those with regressed aneurysm continue to have abnormal coro nary arteries, placing them at ris for premature arteriosclerosis, myo cardial infarction, or both.

Very rarely, aneurysms are see at sites other than coronary ves sels, particularly in large- and me dium-sized muscular arteries. I our series of 200 patients, on child developed axillary aneurysms while about 17% had coronary ar tery aneurysms. Other clinician have reported patients with sever vasculitis of the hands, resulting i gangrene of the fingertips, a com plication that occurs in less thar 1% of Kawasaki patients.

Heart disease, particularly involv ing the coronary arteries, is th most important pathologic chang found in patients who die of Kawa saki syndrome. Less than 5% of fa talities occur during the first 1 days of illness, usually an apparen result of acute pancarditis and peri vasculitis of coronary arteries and the aorta. The most serious cardia complication, massive and fata myocardial infarction, also occur most commonly during the sub acute phase, between 10 and 3 days after onset. About 70% o deaths occur between the eleventh and fiftieth days. H. Fujiwara and Y. Hamashima have tabulated thei pathologic findings in relation t the duration of illness at the time of death (see table on page 106).

Deaths are more common i boys, with a male:female ratio o 3:1. Seventy-five percent of death occur in patients who are less than two years old. We believe that fatal Kawasaki syndrome is identical to what had been previously known as infantile periarteritis nodosa.

Therapy

Effective therapy for Kawasaki syndrome awaits the discovery of its etiology and pathogenesis. At the moment, the best that can be offered patients is supportive therapy as part of a total program of

monitoring for complications.

Aspirin is an attractive therapeutic agent, both for its anti-inflammatory properties and its effectiveness in inhibiting platelet aggregation. The disease does not seem to respond to low or casual doses, but if anti-inflammatory doses of 80 to 100 mg/kg/day are given, the duration of fever is usually reduced by two to three days in the acute phase (from 10 to 11 days down to eight days). When the fever subsides, the aspirin dosage is reduced to less than 10 mg/kg/day.

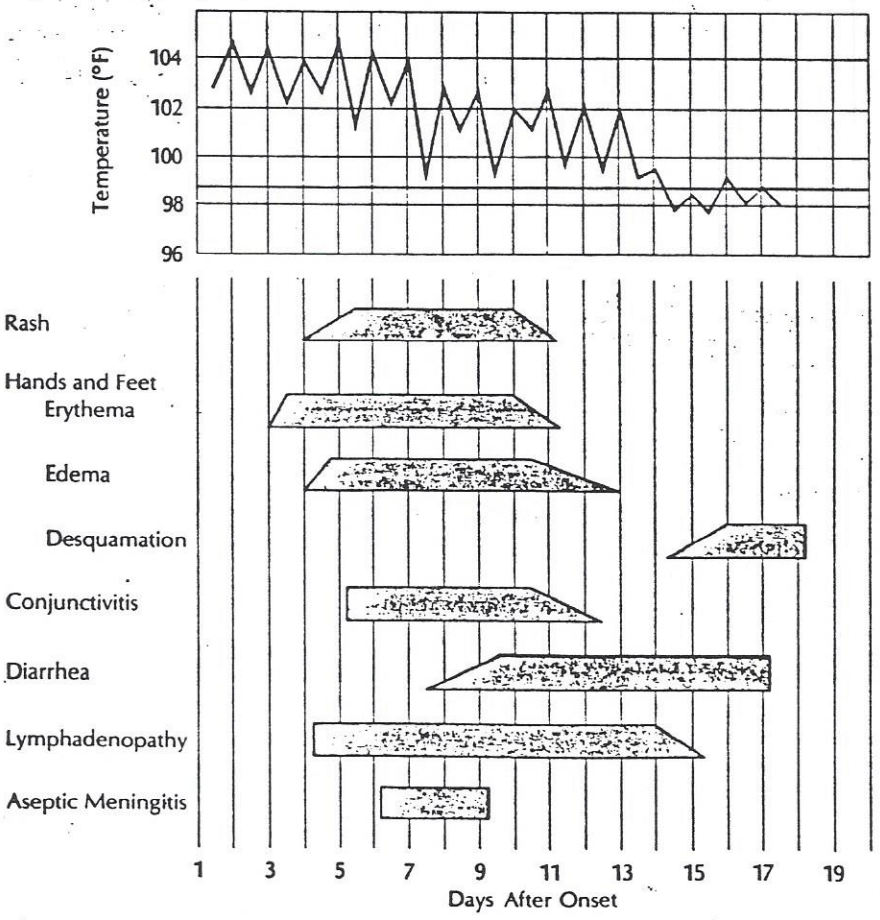
Although fever control may make the patient feel better, it is not the aim of this therapy. The major objective should be to detect and manage congestive heart failure and prevent coronary thrombosis during the period of active coronary vasculitis. The lower aspirin dose will not provide an adequate anti-inflammatory or antipyretic effect, but it is effective in reducing platelet aggregation and does not stimulate vascular thrombogenic factors. Thus, when the fever is under control or when the platelet count rises, it is crucial to reduce the aspirin dosage (as specified above) to prevent thrombosis. Corticosteroids are contraindicated for anti-inflammatory treatment, as they were demonstrated to increase the frequency of aneurysm development in the only controlled study performed to date.

We find it convenient to hospitalize most patients during the acute phase of the disease to facilitate diagnostic testing. Many have been managed successfully as outpatients, however. We feel that a careful follow-up program should be conducted, designed to detect arthritis and cardiac abnormalities. We see our patients twice a week during the second through fourth weeks of illness, and weekly thereafter until the convalescent phase is over. In uncomplicated cases, aspirin therapy is continued until this time, about six to 10 weeks after the initial onset of illness.

As previously noted, patients should be carefully monitored for the development of cardiac disease. We routinely perform M-mode and two-dimensional echocardiography early in the course of the illness, between days seven and 12, and again between days 28 and 35. We believe angiography should be reserved for the further examination of aneurysms detected by echocardiography. Patients with aneurysms should be carefully followed with repeated echocardiographic studies over several years, if necessary, until the lesions resolve. These children should also receive chronic medication, such as aspirin, to suppress platelet aggregation.

Prognosis

For most patients, Kawasaki syndrome is self-limited and nonrecurrent. There is no evidence to date of progressive disease or increased susceptibility to collagen vascular disease or persistent or recurrent arthritis. Cardiac complications sustained during the active period of illness may lead to significant sequelae, such as coronary insufficiency, myocardial infarction, and premature atherosclerosis. It is likely that all children who have had Kawasaki syndrome will have some degree of vascular damage. One fifth will have developed coronary aneurysms by the fourth week after onset. Although aneurysms are known to resolve, the mechanism by which this occurs may involve coagulation, recanalization, and circumferential scarring. We recently conducted what we believe to be the only long-term study involving a significant number of Kawasaki patients, with very disquieting results, which we reported to the American Rheumatism Association last year. We studied 85 children two to nine years



The typical progression of Kawasaki syndrome is illustrated by the course of a nine-month-old Hawaiian-Japanese boy who did not receive anti-inflammatory aspirin therapy. (Adapted from Pediatrics in Review *2:111, 1980)*

after their recovery from the disease. In interviewing them, we carefully refrained from asking leading questions—just, "How are you feeling?" Four of them complained of chest pain, which they described as an oppressive substernal pain (characteristic of angina) when they were running or playing. These children were now of school age, involved in active sports, such as football, soccer, and track.

Follow-up studies revealed some underlying pathology in these and in other, asymptomatic children. Echocardiography and confirmatory coronary angiography showed that two of the children with chest pain had residual coronary aneurysms, as did two children who were asymptomatic. Seven other children had electrocardiographic abnormalities, and one child was hypertensive. The youngsters with chest pain underwent treadmill stress testing; although their ECGs did not change during the procedure, two of them complained of chest pain while exercising. They are being followed by cardiologists.

We were very concerned that 5% of this group—a significant percentage, in our opinion—still have visible residual intrinsic vascular disease so many years after onset and apparent full recovery. Even those children whose aneurysms have apparently resolved probably have abnormal and scarred coronary vessels. We do not know, of course, whether these children will go on to develop premature atherosclerosis or cardiovascular disease in later life. But we feel that this finding imposes on physicians the responsibility of following Kawasaki patients prospectively for a long time after their clinical recovery from the acute episode.

Kawasaki Syndrome Pathologic Findings at Autopsy

Stage I (≤ 10 days after onset)
- Acute perivasculitis of coronary arteries
- Microvascular angiitis of coronary arteries and aorta
- Pancarditis with pericardial, myocardial, endocardial inflammation
- Inflammation with AV conduction system

Stage II (12–28 days after onset)
- Acute panvasculitis of coronary arteries
- Coronary artery aneurysms
- Coronary obstruction and thrombosis
- Myocardial and endocardial inflammation less intense

Stage III (28–45 days after onset)
- Subacute inflammation in coronary arteries
- Coronary artery aneurysms
- Myocardial, endocardial inflammation greatly depressed

Stage IV (50 days after onset)
- Scar formation, calcification in coronary arteries
- Stenosis and recanalization of coronary vessel lumen
- Myocardial fibrosis without acute inflammation

Adapted from H. Fujiwara, Y. Hamashima: *Pediatrics* 61:100, 1978

Etiology

At present, the etiology of Kawasaki syndrome remains unknown. No bacterial agent has been consistently isolated from any site in Kawasaki patients. We have also ruled out involvement of the Leptospira spirochete, and a rickettsial etiology seems doubtful. Viral agents have not been searched for as thoroughly as bacteria, but there is no evidence that any single or unique virus is responsible.

Our speculation is that Kawasaki syndrome is triggered by a common agent(s), which, in certain susceptible children, may stimulate an abnormal immune response leading to a generalized vasculitis and rheumatic involvement of the heart and joints. We have recently found antigen–antibody complexes and immunoregulatory abnormalities in our patients, although the significance of this finding is not yet clear.

The first 15 years' experience with this fascinating symptom complex has led to an understanding of its clinical behavior, pathology, epidemiology, and spectrum of cardiovascular sequelae. We fervently hope that the next decade will witness discovery of the etiology and pathogenesis so that rational preventive and therapeutic strategies can be devised.

Selected Reading

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DEAR DR. GOTT — My grandson is recovering from Kawasaki sickness. What is this disease?

DEAR READER — Kawasaki disease (mucocutaneous lymph node syndrome) is an infectious disease of children. It causes sudden illness with fever, inflamed membranes of the mouth ("strawberry tongue"), a diffuse rash (which later peels), joint pain, diarrhea, pneumonia and swollen lymph glands. Unfortunately, the heart and its blood vessels can become inflamed; more than 80 percent of children develop cardiac complications of Kawasaki disease, sometimes as long as several years after the acute illness.

In 1986, experts studying the mucocutaneous lymph node syndrome were struck by a strange similarity: Under a microscope, the children's blood vessels showed the same type of inflammation seen in the arteries of adults with a disease called periarteritis nodosa. In this condition, the walls of blood vessels become acutely inflamed and weakened; blood clots (thromboses) may adhere to the irritated linings. Although the cause of Kawasaki disease is still unknown, evidence suggests that it could be a juvenile form of periarteritis. Perhaps the syndrome actually includes several types of similar diseases.

At present the only treatment for Kawasaki disease is aspirin. Recently, specialists at Children's Hospital in Boston have recommended intravenous gamma globulin to prevent cardiac complications. Ordinarily, consequences of the inflammation are treated as they appear. The disease occurs worldwide. In 1981, epidemics were reported in Massachusetts and in Rochester, N.Y. Many scientists are trying to discover exactly what Kawasaki disease is. To date, the illness still shrouded in mystery.

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