Kawasaki Disease: A Brief History

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ABSTRACT. Tomisaku Kawasaki published the first English-language report of 50 patients with Kawasaki disease (KD) in 1974. Since that time, KD has become the leading cause of acquired heart disease among children in North America and Japan. Although an infectious agent is suspected, the cause remains unknown. However, significant progress has been made toward understanding the natural history of the disease and therapeutic interventions have been developed that halt the immune-mediated destruction of the arterial wall. We present a brief history of KD, review progress in research on the disease, and suggest avenues for future study.

Kawasaki saw his first case of KD in January 1961 and published his first report in Japanese in 1967. Whether cases existed in Japan before that time is currently under study. The most significant controversy in the 1960s in Japan was whether the rash and fever sign/symptom complex described by Kawasaki was connected to subsequent cardiac complications in a number of cases. Pathologist Noboru Tanaka and pediatrician Takajiro Yamamoto disputed the early assertion of Kawasaki that KD was a self-limited illness with no sequelae. This controversy was resolved in 1970 when the first Japanese nationwide survey of KD documented 10 autopsy cases of sudden cardiac death after KD. By the time of the first English-language publication by Kawasaki in 1974, the link between KD and coronary artery vasculitis was well-established.

KD was independently recognized as a new and distinct condition in the early 1970s by pediatricians Marian Melish and Raquel Hicks at the University of Hawaii. In 1973, at the same Hawaiian hospital, pathologist Eunice Larson, in consultation with Benjamin Landing at Los Angeles Children’s Hospital, retrospectively diagnosed a 1971 autopsy case as KD. The similarity between KD and infantile periarteritis nodosa (IPN) was apparent to these pathologists, as it had been to Tanaka earlier.

What remains unknown is the reason for the simultaneous recognition of this disease around the world in the 1960s and 1970s. There are several possible explanations. KD may have been a new disease that emerged in Japan in the 1960s and 1970s. There are several possible explanations. KD may have been a new disease that emerged in Japan in the 1960s and 1970s. Alternatively, KD and IPN may be part of the spectrum of the same disease and clinically mild KD masqueraded as other diseases, such as scarlet fever in the preantibiotic era. Case reports of IPN from Western Europe extend back to at least the 19th century, but, thus far, cases of IPN have not been discovered in Japan before World War II. Perhaps the factors responsible for KD were introduced into Japan after the World War II and then emerged in a more virulent form that subsequently spread through the industrialized Western world. It is also possible that improvements in health care and, in particular, the use of antibiotics to treat infections caused by organisms including toxin-producing bacteria reduced the burden of rash/fever illness and allowed KD to be recognized as a distinct clinical entity.

Itsuzo Shigematsu, Hiroshi Yanagawa, and colleagues have conducted 14 nationwide surveys in Japan. These have indicated that: 1) KD occurred initially in nationwide epidemics but now occurs in regional outbreaks; 2) there are ~5000 to 6000 new cases each year; 3) current estimates of incidence rates are 120 to 150 cases per 100 000 children <5 years old; 4) KD is 1.5 times more common in males and 85% of cases occur in children <5 years old; and 5) the recurrence rate is low (4%). In 1978, David Morens at the Centers for Disease Control and Prevention published a case definition based on Kawasaki’s original criteria. The Centers for Disease Control and Prevention developed a computerized database in 1984, and a passive reporting system currently exists in 22 states. Regional investigations and national surveys suggest an annual incidence of 4 to 15 cases per 100 000 children <5 years of age in the United States.

The natural history of KD reveals that coronary artery aneurysms occur as a sequela of the vasculitis in 20% to 25% of untreated children. Echocardiography can be successfully used to detect coronary artery dilatation and aneurysms in virtually all patients. Patients with no acute phase coronary artery changes detected by echocardiogram are clinically asymptomatic at least 10 years later. The Japanese Ministry of Health has established a registry of 6500 children who will be followed longitudinally to determine the natural history of the illness. No similar registry of patients exists in the United States.

Studies of KD pathogenesis show a progression of arterial lesions accompanying KD vasculitis and a number of immunoregulatory changes, including a deficiency of circulating CD8+ suppressor/cytotoxic T cells; an abundance of circulating B cells spontaneously producing immunoglobulin; and circulating, activated monocytes. Biochemical and immunologic evidence suggests endothelial cell activation and injury. Although the cause of KD remains unknown, clinical trials have established effective therapies, despite the absence of a proven cause.

Intravenous immunoglobulin (IVIG) plus aspirin lowers the rate of coronary artery aneurysms from 20% to between 3% and 5%. In 1988, the Committee on Infectious Diseases of the American Academy of Pediatrics endorsed IVIG treatment as recommended therapy for KD. Questions remain regarding treatment of patients who fail to respond to an initial dose of IVIG. The role of...
steroids or other antiinflammatory agents in the treatment of KD is controversial.

Areas for further research include: 1) a more sensitive case definition that includes laboratory and echocardiographic data, as well as clinical signs and symptoms; 2) development of a diagnostic test based on the biology of inflammation and acute endothelial cell damage that, in the absence of the causative agent, could be used to identify children with KD; 3) studies of index cases and their families to identify relevant genetic factors; and 4) long-term follow-up of patients into their third and fourth decades with monitoring for late cardiovascular sequelae. Pediatrics 2000;106(2). URL: http://www.pediatrics.org/cgi/content/full/106/2/e27; vasculitis, coronary artery aneurysms, pediatric cardiology.

ABBREVIATIONS. KD, Kawasaki disease; MCOS, mucocutaneous ocular syndrome; IPN, infantile periarteritis nodosa; IgA, immunoglobulin A; IVIG, intravenous immunoglobulin.

In 1974, Dr Tomisaku Kawasaki first reported in English his original series of 50 Japanese patients who manifested a constellation of signs and symptoms that would later bear his name. In the intervening 25 years, Kawasaki disease (KD) has been reported in children of most racial and ethnic groups throughout the world and is now the leading cause of acquired heart disease in children in the United States and Japan. Although an infectious agent is suspected, the cause of this puzzling disease remains unknown. Over the last 25 years, however, significant progress has been made toward understanding the pathogenesis of the vasculitis, the natural history of the disease, and therapeutic interventions that halt the immune-mediated destruction of the arterial wall. This review will highlight the insights that have been gained and the challenges that remain in our study of this disease.

Emergence of KD in Japan
Kawasaki saw his first case of KD in January 1961 when he was a staff pediatrician at the Red Cross Hospital in a suburb of Tokyo (T. Kawasaki, personal communication, 1998). The patient, a 4-year-old boy, recovered spontaneously from his illness and was discharged as “diagnosis unknown” (Fig 1). It was not until Kawasaki saw his second case 1 year later that he began to suspect the emergence of a disease that had not been previously described in Japan. In fact, cases now thought to be KD were documented in Japan as early as the 1950s. Whether cases existed in Japan before that time is currently under investigation as part of the Kawasaki Disease History Project. Initially, Kawasaki believed that the clinical syndrome was a benign, self-limited process with no sequelae. He reported the first 7 cases as “non-scarlet fever syndrome with desquamation” at a 1962 meeting of the Chiba District Pediatric Group of the Japanese Pediatric Association in Chiba. By 1964, he had gathered 22 cases and these he presented as mucocutaneous ocular syndrome (MCOS) at the annual meeting of the East Japan/Chubu Pediatric Group. Despite the accumulation of cases, many clinicians continued to believe that KD was not a new disease entity, but rather an atypical form of Stevens-Johnson syndrome (T. Kawasaki, personal communication, 1998). In 1965, Dr Noboru Tanaka, then head of the Department of Pathology at the Red Cross Hospital, performed an autopsy on a child previously diagnosed by Kawasaki as having MCOS. The child had died suddenly and unexpectedly and at autopsy Tanaka discovered coronary artery thrombosis. Tanaka, thus, was the first pathologist to recognize the serious and sometimes fatal cardiac complications of the disease. Despite the autopsy evidence, most clinicians rejected the claim of Tanaka that the disease called MCOS could be associated with fatal cardiac complications (N. Tanaka, personal communication, 1999). At the urging of Dr Fumio Kosaki, then head of the Department of Pediatrics at Red Cross Hospital, Kawasaki published his series of 50 patients in an allergy journal to avoid conflict with individuals in the pediatric establishment who disagreed with his claim that he was describing a previously unknown and unique condition.

The publication of the article by Kawasaki engendered considerable excitement and controversy throughout the Japanese medical community. Probably the most significant clinical debate that ensued was over the possible link between the rash and fever sign/symptom complex Kawasaki had so carefully documented and the cardiac complications of this condition. The first clinician to suspect cardiac involvement in nonfatal cases of KD was Dr Takajiro Yamamoto, head of the Department of Pediatrics at St Luke’s Hospital in Tokyo (T. Yamamoto, personal communication, 1998). He, like Kawasaki, had been independently gathering cases in the late 1950s and early 1960s. In December 1966, one of his patients presented with the clinical stigmata of typical KD and had a gallop rhythm associated with congestive heart failure. In 1968, Yamamoto and colleagues published a report of 23 patients, of whom 11 (48%) had abnormalities detected by electrocardiogram. These results persuaded Yamamoto that cardiac involvement was a common feature of this syndrome.

It is possible that Yamamoto was the first physician to recognize KD in the United States, when, as a visiting professor at New York Cornell Hospital in 1963, he observed a patient with the KD sign/symptom complex while attending Professors’ Rounds led by Dr Heinz Eichenwald, then acting Chairperson of the Department of Pediatrics (T. Yamamoto, personal communication, 1998; H. Eichenwald, personal communication, 1999). Because of Yamamoto’s experiences with similar patients in Japan, he recognized the clinical features of the condition that would later become known as KD.

Not until 1970, however, was it possible to shed new light on the debate about the cardiac sequelae of KD. The first Japanese nationwide epidemiologic survey of KD was conducted in that year by Dr Itsuzo Shigematsu (Chief of the Department of Epidemiology, Institute of Public Health, Tokyo) and colleagues. At the urging of Tanaka, the questionnaire asked about cardiac complications associated with the clinical syndrome. With this extensive sur-
vey, the number of cases and the range of variation in the condition raised the discussions about the disease to new levels of sophistication. Confirming the earlier arguments of both Tanaka and Yamamoto, it became clear that cardiac involvement, as a sequela of severe vasculitis, was part of the spectrum of KD. By the time of the first English-language publication of Kawasaki’s original 50 patients in 1974, the link between KD and coronary artery vasculitis had been well-established.

A separate debate during these early days of KD research involved pathologists who saw a similarity between infantile periarteritis nodosa (IPN) and fatal KD and questioned whether these were the same disease. As a result of the 1970 national survey in Japan, 10 autopsy cases of sudden death after KD were compiled, and it became apparent that there were good reasons to pursue links to IPN.12 Tanaka et al13 published a discussion of the possible link between the 2 disease entities in 1972. Following his lead, Dr Zenshiro Onouchi, then a staff pediatrician at Kyoto Municipal Medical School, and his pathology colleagues presented further autopsy data suggesting that the fatal syndrome IPN might be a severe form of KD.14

Emergence of KD in the United States

What we now know as KD was also being noticed in Hawaii at the same time that it was being described in Japan. In the early 1970s, 2 young faculty members in the Department of Pediatrics at the University of Hawaii began to see children with an unusual constellation of fever, rash, and red mucous membranes. Dr Marian Melish, a specialist in pediatric infectious diseases, and Dr Raquel Hicks, a pediatric rheumatologist, were puzzled by this illness that occurred predominantly among Asian children, most of them Japanese Americans (M. Melish, personal communication, 1999). These cases reminded Melish of 2 patients who she had seen in the late

Fig 1. Clinical description of the first case of Kawasaki. The patient was a 4-year-old Japanese boy who was hospitalized on the sixth day of illness in January 1961 with fever and associated signs and symptoms. An unusual feature of this patient was the Coombs-positive hemolytic anemia that Kawasaki never saw again in subsequent patients with the clinical syndrome. Temperatures are in degrees centigrade; im indicates intramuscularly; iv, intravenously; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASLO, antistreptolysin O; Hb, hemoglobin concentration; R, red blood cell count; W, white blood cell count; E, eosinophils; B, basophils; St, immature neutrophils (stabs); Seg, neutrophils; L, lymphocytes; M, monocytes; II, icterus index; TB, total bilirubin; Dir, direct bilirubin; Ind, indirect bilirubin. Adapted from Kawasaki (N. Tanaka, personal communication, 1999); translation by Chisato Shimizu.
KD Around the World

The reason for the simultaneous recognition of this disease around the world in the 1960s and 1970s remains unknown. There are several possible explanations. KD may have been a new disease that emerged in Japan and emanated to the Western world through Hawaii, where the disease became prevalent among Asian children. Alternatively, KD and IPN may be part of the spectrum of the same disease and clinically mild KD masqueraded as other diseases, such as scarlet fever in the preantibiotic era. Case reports of IPN from Western Europe extend back to at least the 19th century, but, thus far, cases of IPN have not been discovered from Japan before World War II. Perhaps the factors responsible for KD were introduced into Japan after the war and then reemerged in a more virulent form that subsequently spread through the industrialized Western world. It is also possible that improvements in health care and, in particular, the use of antibiotics to treat infections caused by organisms including toxin-producing bacteria reduced the burden of rash/fever illness and allowed KD to be recognized as a distinct clinical entity.

Understanding the Epidemiology

In 1970, a meeting of Japanese physicians and epidemiologists was organized by the Japanese Ministry of Health and was led by Shigematsu and colleagues to design a case definition for KD and to conduct a nationwide survey of the disease. A color brochure with pictures of the clinical features of KD and a brief questionnaire were distributed to all hospitals with at least 100 beds and a department of pediatrics. A total of 631 hospitals responded and >3000 cases were reported dating back to the early 1950s. To date, 14 nationwide surveys have been conducted by Dr Hiroshi Yanagawa (Chief of the Department of Public Health, Jichi Medical School, Tochigi) and colleagues in Japan. From this enormous database, we have learned that: 1) recognized cases of KD occurred initially in nationwide epidemics (1979, 1982, and 1986) but now occur only in limited, regional epidemics, 2) there are ~5000 to 6000 newly diagnosed cases per year in Japan, 3) current estimates of incidence rates are between 120 and 150 cases per 100 000 children <5 years old, 4) the disease is 1.5 times more common in males than in females and 85% of cases occur in children <5 years old, and 5) the recurrence rate is low (4%).

Although it is beyond the scope of this review to summarize the international literature on KD, reports from around the world suggest that where there are children, there is KD. Whether the global recognition of KD represents the emergence of a new disease in these countries or simply represents the unmasking of a disease process that was hidden in other disease categories must ultimately await elucidation of the causative agent.

In the United States, a modified case definition based on Kawasaki's original clinical criteria, and with the exclusion of other plausible causes of fever (Table 1), was created in 1978 by Dr David Morens, then an officer of the Epidemiologc Investigation Service at the Centers for Disease Control and Prevention. Beginning in 1984, a computerized database was created at the Centers for Disease Control and Prevention. A passive reporting system for KD in 22 states is currently in place, but poor compliance with reporting procedures has prevented an accurate estimate of the number of cases diagnosed each year. However, local investigations in different regions of the continental United States coupled with national surveys suggest an annual incidence of 4 to 10 cases per 100 000 children <5 years old.

### TABLE 1. Diagnostic Criteria for Kawasaki Disease*

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<td>1</td>
<td>Fever ≥ 5 d</td>
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<td>2</td>
<td>Bilateral conjunctival injection</td>
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<td>3</td>
<td>Changes of the mucous membranes of the upper respiratory tract: injected pharynx, injected, fissured lips, strawberry tongue</td>
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<td>4</td>
<td>Changes of the peripheral extremities: peripheral edema, peripheral erythema, periungual desquamiation</td>
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<tr>
<td>5</td>
<td>Polymorphous rash</td>
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<tr>
<td>6</td>
<td>Cervical adenopathy</td>
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* Adapted from Morens and O'Brien.25
will develop coronary artery stenosis and may sub-
due to the acute disease is uncertain.
without evidence of coronary artery abnormalities
myointimal proliferation in the coronary and other
lesions in KD based on the duration of illness before
dish the following features of the natural history of
Understanding the Natural History
Large series of patients from Japan have estab-
lished the following features of the natural history of
Understanding the Pathogenesis
Careful descriptive studies of autopsy cases have
suggested the following progression of the arterial
lesions in KD based on the duration of illness before
death Stage I (0–9 days) is characterized by
perivasculitis of small arteries. Pericarditis, myocarditis, inflammation of the atrioventricular conduc-
tion system, and endocarditis with valvulitis are also
present. Stage II (12–25 days) is characterized by
pan-vasculitis of medium-sized, muscular arteries
with aneurysm formation and thrombosis. Myocarditis, pericarditis, and endocarditis with valvulitis
may also be present. During stage III (28–31 days),
myointimal proliferation in the coronary and other
medium-sized arteries is prominent, and acute in-
flammation disappears from the microvasculature.
In stage IV (after 40 days), scarring of arteries with
stenosis may occur.
The acute vasculitis of KD is associated with a
number of immunoregulatory changes. Dr Donald
Leung, then an assistant professor at Harvard Medical
School, was the first to demonstrate the de-
ciency of circulating CD8+ suppressor/cytotoxic T
cells and the abundance of circulating activated B
cells engaged in the spontaneous production of
immunoglobulins.50 Dr Susumu Furukawa (then Pro-
fessor of Pediatrics at Juntendo University Medical
School) and coworkers51,52 studied the activation of
circulating monocytes during the acute phase. Acti-
vation of cellular elements of the immune system is
likely to be fueled by proinflammatory cytokines,
which are elevated during the acute phase.53–55 Sev-
eral lines of evidence suggest that genetic influences
on the magnitude and nature of the immune re-
response may underlie the susceptibility to KD.56,57
Biochemical and immunologic evidence suggest
endothelial cell activation and injury. Increased ex-
pression of cell adhesion molecules may increase the
recruitment of immune effector cells at the luminal
surface of the arteries.58,59 Other likely mechanisms
of endothelial cell injury include antibodies directed
against activated endothelial cells60 and increased
levels of vascular endothelial cell growth factor,
which may also be important in vessel repair.61
Dr Anne Rowley (Professor of Pediatrics, North-
western University) and colleagues62 are investigat-
ing the role of the immunoglobulin A (IgA) immune
response in KD patients. They propose a mucosal
portal of entry for the agent, which then elicits a
specific IgA response. The role of IgA-secreting B
cells detected in some autopsy tissues is currently
under investigation.
Search for the Causative Agent
The cause of KD remains unknown, although an
infectious agent is likely in view of the following
observations: 1) a seasonal peak in the winter/spring
months in most geographic areas, 2) epidemics with
a clear epicenter, 3) the peak incidence in the toddler
age group with only rare cases in infants <3 months
old and in adults, suggesting a role for transplacental
antibodies conferring protection coupled with
asymptomatic infection in most individuals with de-
velopment of protective antibodies, and 4) the simi-
larity of many of the clinical features of KD to other
infectious diseases, eg, adenoviral infection and scar-
et fever. A long list of discarded pathogens is all that
remains after 30 years of search for the causal agent
of KD. Initially, standard microbiologic methods to
isolate pathogens from different body fluids as well
as animal inoculation of these specimens were used
in an attempt to isolate an agent.9,16 More recently,
molecular methods to detect agent-specific nucleic
acid in patient samples and subtractive hybridization
using acute and convalescent patient samples to
identify specific antigen antibodies have not yet
yielded answers63 (J.C.B., unpublished data). Finally,
the idea that bacterial toxins acting as superantigens
could trigger the cascade of events that lead to KD has been widely debated. This controversial hypothesis has been supported by some studies and refuted by others.

Research efforts have recently focused on identifying a diagnostic test for the disease in lieu of actually identifying the causative agent. This would be analogous to the use of the heterophil antibody test to diagnose infectious mononucleosis before the discovery of the Epstein-Barr virus. As part of this effort, studies are testing the hypothesis that measurement of metalloproteinases in acute serum might serve as a discriminatory diagnostic marker of KD.

Therapy

In the original series of 50 patients, Kawasaki attempted therapy with different antibiotics (penicillins, chloramphenicol, and tetracycline), steroids, and aspirin without a dramatic effect on the clinical course of the disease. After the publication of successful intravenous immunoglobulin (IVIG) therapy of idiopathic thrombocytopenic purpura in 1981, 2 Japanese investigators, Dr Kensi Furusho (then Professor of Pediatrics, Kokura Memorial Hospital, Kitakyushu City) and Dr Susumu Furukawa (then Assistant Professor of Pediatrics, Juntendo University School of Medicine, Tokyo) independently tried high-dose IVIG therapy in acute KD patients (K. Furusho and S. Furukawa, personal communication, 1999). Following the lead from the Japanese, a US multicenter study group was formed and 2 trials of high-dose IVIG therapy for acute KD were conducted in the United States. The results of these trials and further trials in Japan established that IVIG plus aspirin lowered the rate of coronary artery aneurysms from 20% to between 3% and 5%. In addition, a single dose of 2-g IVIG/kg resulted in more rapid cessation of fever and improvement in laboratory parameters of systemic inflammation. In 1988, the Committee on Infectious Diseases of the American Academy of Pediatrics endorsed IVIG treatment as recommended therapy for children with acute KD. More recently, questions have arisen regarding treatment of patients who fail to respond with cessation of fever after the first dose of IVIG and whether steroids or other antiinflammatory agents should play a greater role in the initial control of inflammation in these patients.

Future Directions

Today, the Japan Kawasaki Disease Research Center in Tokyo, Japan, founded by Kawasaki in 1980, serves as an important resource for information about KD as well as a catalyst for Japanese and international research efforts and education. Clearly, the primary mystery of KD is the cause of the disease. Although an infectious agent is suspected, the culprit pathogen continues to elude investigators. Even in the absence of knowledge of the causative agent, a sensitive and specific diagnostic test would greatly aid studies of epidemiology, outcome, and treatment of KD.

We suggest that fruitful avenues for future research include the following: 1) detailed investigation of the global incidence of the disease, 2) institution of sentinel hospital surveillance for KD and creation of national registries, 3) a more sensitive case definition that includes laboratory and echocardiographic data as well as clinical signs and symptoms, 4) long-term follow-up of patients into their third and fourth decade with monitoring for late cardiovascular sequelae, 5) expanded studies of the pathology of arteries in patients dying of other causes after KD, 6) studies of index cases and their families to identify genetic factors that may influence disease susceptibility and outcome, 7) application of new molecular-based methods to search for the causative agent, 8) increased cooperation between clinicians and pathologists with creation of a centralized registry of autopsy tissues that could quickly and efficiently be accessed for testing new hypotheses, 9) development of a diagnostic test based on the biology of inflammation and acute endothelial cell damage that, in the absence of the causative agent, could be used to identify children with the disease, and 10) international, collaborative, multicenter prospective trials of additional antiinflammatory therapies for the acute disease and antithrombotic and thrombolytic therapies for children with aneurysms.

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