



Kawasaki's syndrome

Background

This syndrome has also been termed *mucocutaneous lymph node syndrome* and *Kawasaki's disease*. It has been classified as a vasculitis because of its occasionally lethal vascular complications. It is a disease affecting infants and children although adult cases have been reported. There is fever, non-exudative conjunctivitis, cervical lymphadenopathy, oropharyngeal inflammation, thrombocytosis, and vasculitis. The vasculitis may involve the coronary arteries which may lead to aneurysm or thrombosis in 20% of cases. In 1% of cases, this may be fatal. There may be epidemic outbreaks suggesting an infectious vector.

The skin findings are prominent and include an erythematous rash with edema and erythema of the palms and soles. With time, there is desquamation of the tips of the fingers and toes. There may be a desquamating perineal rash and a pustular rash.

Because of its resemblance to staphylococcal and streptococcal infections, a microbiological etiology has been suspected. However, to date, no cause has been found. A combination of aspirin and intravenous gamma globulin has been used successfully to treat patients, dramatically reducing the incidence of coronary artery thrombosis.

The current diagnostic criteria are as follows:

Diagnostic Criteria

(Need 5 of 6, with fever an absolute, must be present for diagnosis of classic Kawasaki's disease)

Fever, lasting more than 5 days and refractory to appropriate antibiotic therapy

Polymorphous erythematous rash

Nonpurulent conjunctival injection, bilateral

Oropharyngeal changes, including diffuse hyperemia, strawberry tongue, lip changes (swelling, fissuring, erythema)

Peripheral extremity changes, including erythema, edema, induration, and desquamation

Nonpurulent cervical lymphadenopathy

Other Findings

Cardiac-coronary aneurysms, pericardial effusion, myocarditis, CHF

CNS-aseptic meningitis, facial palsy, cerebral infarction

Renal-sterile pyuria, proteinuria, nephritis

Joint involvement (arthralgias or arthritis)

Pulmonary-pleural effusion, infiltrates

GI-abdominal pain, diarrhea, hepatitis, obstructive jaundice, hydrops

Ophthalmologic-conjunctivitis, uveitis

Peripheral extremity gangrene

It should be noted that up to 10-45% of published cases have incomplete or atypical clinical presentations. The two most commonly missing findings are cervical lymphadenopathy and polymorphous rash.

EPIDEMIOLOGY	CHARACTERIZATION
SYNONYMS	Mucocutaneous lymph node syndrome Kawasaki's disease
INCIDENCE	Most common cause of acquired heart disease in children in the United States and Japan
<p>Results of 12 nationwide epidemiological incidence surveys of Kawasaki disease in Japan.</p> <p>Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H.</p> <p>Department of Public Health, Jichi Medical School, Tochigi-ken, Japan.</p>	<p>Arch Pediatr Adolesc Med 1995 Jul;149(7):779-83 Abstract quote</p> <p>OBJECTIVE: To describe the long-term trend of incidence and other epidemiological pictures of Kawasaki disease in Japan, by using the results of 12 nationwide epidemiological surveys on Kawasaki disease that have been conducted throughout Japan (ie, surveys that have encompassed the pediatric departments of hospitals with more than 100 beds) every 2 years since 1970.</p> <p>RESULTS: At the end of December 1992, the total number of patients with this disease was 116,848 (males, 67,815; females, 49,033; male-female ratio, 1.38). The number of cases increased year by year, with three outbreaks in 1979, 1982, and 1986. There have been no cyclical changes since 1986. The incidence was higher in males and in those children who were 1 year of age or younger. The fatality rate decreased from 1% in 1974 to 0.04% in 1992.</p> <p>CONCLUSIONS: The patterns of descriptive epidemiology, such as seasonality and cyclical changes in incidence, supported the theory of an infectious agent as the causal agent. However, the incidence data since 1986 provide less support for an infectious theory.</p>
<p>Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan.</p>	<p>Pediatrics 1998 Dec;102(6):E65 Abstract quote</p> <p>OBJECTIVE: The objective of the study is to describe recent epidemiologic patterns of Kawasaki disease based on information included in patient records that had been obtained through a nationwide hospital survey in Japan.</p>

Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Tanihara S, Oki I, Zhang T.

Department of Public Health, Jichi Medical School, Tochigi, Japan.

METHODS: A questionnaire and diagnostic criteria for Kawasaki disease that had been approved by the Kawasaki Disease Research Committee were sent to all pediatric departments of hospitals (2638 hospitals) with a bed capacity of at least 100. The subjects all were new patients who were treated during a 2-year period from 1995 to 1996.

RESULTS: A total of 12 531 children contracted the disease during the observation period. The incidence was 102.6 for 1995 and 108.0 for 1996 per 100 000 children younger than age 5 years. The male:female ratio was 1.37. The age distribution pattern showed a peak near 6 months of age. Geographic variations in the incidence suggested the existence of local outbreaks. Cardiac sequelae were seen in 12% of the patients.

CONCLUSION: More than 6000 patients suffered from Kawasaki disease each year, and its annual incidence is increasing steadily. The probable existence of local outbreaks is worthy of note. Other epidemiologic patterns were unchanged from previous years.

An evaluation of hospitalizations for Kawasaki syndrome in Georgia.

Gibbons RV, Parashar UD, Holman RC, Belay ED, Maddox RA, Powell KE, Schonberger LB.

Division for Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Mail Stop A-39, 1600 Clifton Rd NE, Atlanta, GA 30333, USA.

Arch Pediatr Adolesc Med 2002 May;156(5):492-6 Abstract quote

OBJECTIVE: To evaluate and describe the epidemiologic characteristics of Kawasaki syndrome (KS) hospitalizations in Georgia.

DESIGN: We reviewed hospital discharge data and corresponding medical records for Georgian patients discharged with a KS diagnosis during 1997 and 1998.

RESULTS: During the study period, 233 KS hospital discharges were recorded in Georgia; 177 (76%) were for children younger than 5 years. Twenty-one (9%) of 233 of the hospital discharges represented multiple hospitalizations. Medical records for 211 KS discharges (91%), representing 197 patients (93%), were reviewed. For those 189 patients whose medical records were reviewed and had sufficient information, 139 (74%) either had a documented illness that met the Centers for Disease Control and Prevention (CDC) definition for KS (n = 135) or had coronary artery abnormalities without meeting the CDC definition for KS (atypical KS; n = 4). Eight patients had only a history of KS. Excluding multiple

	<p>hospitalizations and patients with only a history of KS, 158 hospitalizations were for patients younger than 5 years (14.0 per 100 000 children); 110 of these patients met the KS or atypical KS definition (9.8 per 100 000 children).</p> <p>CONCLUSIONS: Hospital discharge data are useful for KS surveillance. However, analysis of hospital discharge data may slightly overestimate the KS hospitalization rates because some discharges may represent multiple hospitalizations or hospitalizations of patients with only a history of KS. The incidence and epidemiology of KS in Georgia are consistent with findings from other continental US studies. Physicians should exercise their best clinical judgment in identifying and treating patients with KS who may not meet standard case definitions.</p>
<p>AGE RANGE-MEDIAN</p>	<p>80% occur <5 years Peak <2 years</p>
<p>GEOGRAPHY</p>	<p>United States Japan</p>
<p>A nationwide incidence survey of Kawasaki disease in 1985-1986 in Japan.</p> <p>Yanagawa H, Nakamura Y, Yashiro M, Fujita Y, Nagai M, Kawasaki T, Aso S, Imada Y, Shigematsu I.</p> <p>Department of Public Health, Jichi Medical School, Tochigi-ken, Japan.</p>	<p>J Infect Dis 1988 Dec;158(6):1296-301 Abstract quote</p> <p>Nationwide epidemiological surveys of Kawasaki disease have been conducted nine times in Japan since 1970. By the end of 1986, 83,857 (male:female ratio, 1.4) cases were reported.</p> <p>We summarize the results of these surveys, especially the latest survey of cases from January 1985 to December 1986. There were three epidemic years - 1979, 1982, and 1986. The ratios of the number of patients diagnosed in each of those years to the number in the preceding year were 2.0, 2.4, and 1.7, respectively. The last epidemic started in a metropolitan area of Tokyo in December 1985 and propagated northwards and southwards to involve almost all of the country in six months. The age-specific incidence curve showed a unimodal peak at nine to 11 months of age.</p> <p>The proportion of sibling cases was approximately 2%. The epidemiological pictures suggested that the disease was caused by an unknown biologic agent that is common in the community and that spreads easily among very young children.</p>

<p>Relationship of climate, ethnicity and socioeconomic status to Kawasaki disease in San Diego County, 1994 through 1998.</p> <p>Bronstein DE, Dille AN, Austin JP, Williams CM, Palinkas LA, Burns JC.</p> <p>Department of Pediatrics, University of California, San Diego, USA.</p>	<p>Pediatr Infect Dis J 2000 Nov;19(11):1087-91 Abstract quote</p> <p>BACKGROUND: Kawasaki disease (KD) is the most common cause of acquired heart disease in children in the United States. By monitoring trends in patient numbers and demographics during a 5-year period, we were able to explore the relationship between climate, ethnicity, socioeconomic status and susceptibility to KD.</p> <p>METHODS: We conducted active surveillance for all patients hospitalized with KD in San Diego County from 1994 through 1998. Data on seasonal variation in monthly rainfall and temperature were obtained from the US Meteorological Service. Patient sex, age, date of admission and self-reported ethnicity were identified from patient medical records. Socioeconomic status was assessed on the basis of insurance status among patients hospitalized at a single institution.</p> <p>RESULTS: During the 5-year period there were 169 cases of KD in San Diego County. The overall annual incidence of KD in children < 5 years of age ranged from 8.0 to 15.4/100 000. KD incidence was inversely associated with average monthly temperature ($r = -0.47, P < 0.001$) and positively associated with average monthly precipitation ($r = -0.52, P < 0.001$). Asian/Pacific Islanders < 5 years of age were 2.7 times as likely and Hispanics were one-third as likely to be hospitalized for KD than children from all other ethnic groups combined. Children with private or military insurance in all ethnic groups were more likely to have a diagnosis of KD than children with government assistance or no insurance. After controlling for insurance status, only Asian/Pacific Islanders remained at increased risk (rate ratio, 2.14) for KD relative to all other ethnic groups combined.</p> <p>CONCLUSION: KD is a common childhood vasculitis of unknown etiology. The skewed ethnic distribution and seasonality are consistent with the hypothesis that KD is an infectious disease that is influenced by environmental and genetic factors.</p>
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DISEASE ASSOCIATIONS	CHARACTERIZATION
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HIV	
<p>Kawasaki-like syndromes associated with human immunodeficiency virus infection.</p> <p>Johnson RM, Little JR, Storch GA.</p> <p>Division of Infectious Diseases, Washington University School of Medicine, St. Louis, MO 63110, USA.</p>	<p>Clin Infect Dis 2001 Jun 1;32(11):1628-34 Abstract quote</p> <p>Kawasaki disease is an acute febrile vasculitic syndrome of early childhood. It is very rarely seen in adults. Among the adult patients with Kawasaki disease who have been described, a disproportionate number are infected with human immunodeficiency virus (HIV). This suggests that the immunocompromised state may predispose individuals to this syndrome.</p> <p>We report our experience with 2 HIV-positive patients who presented with Kawasaki-like syndromes and review the published literature on HIV-positive patients with similar syndromes.</p>

PATHOGENESIS	CHARACTERIZATION
Unknown	<p>Superantigen? Virus? Bacteria?</p>
MATRIX METALLOPROTEINASES	
<p>Circulating matrix metalloproteinases and their inhibitors in patients with Kawasaki disease.</p> <p>Senzaki H, Masutani S, Kobayashi J, Kobayashi T, Nakano H, Nagasaka H, Sasaki N, Asano H, Kyo S, Yokote Y.</p> <p>Departments of Pediatric Cardiology and Pediatrics, Saitama Heart Institute, Saitama Medical School</p>	<p>Circulation 2001 Aug 21;104(8):860-3 Abstract quote</p> <p>BACKGROUND: Accelerated matrix breakdown caused by the increased activity of matrix metalloproteinases (MMPs) and/or the quantitative imbalance between MMP and tissue inhibitor of MMP (TIMP) have been implicated in several pathological conditions. MMP and TIMP may also be involved in the destruction of the coronary arterial wall and the resultant coronary arterial lesions in Kawasaki disease.</p> <p>METHODS AND RESULTS: Plasma levels of MMPs, neutrophil elastase, and TIMPs were measured by enzyme-linked immunoassay in 57 patients with Kawasaki disease and no coronary arterial lesions (group 1) and in 8 patients with Kawasaki disease and coronary arterial</p>

<p>Hospital, Saitama, Japan.</p>	<p>lesions (group 2). Blood samples were obtained before and after intravenous gamma globulin therapy and in the convalescent stage. Levels of MMPs, neutrophil elastase, and TIMPs were significantly higher in Kawasaki disease patients before gamma globulin therapy than in 18 age-matched afebrile control subjects and 17 age-matched febrile disease control subjects ($P<0.01$). More importantly, the pre-gamma globulin MMP9 level and MMP9/TIMP2 ratio and post-gamma globulin MMP3 level and MMP3/TIMP1 ratio were significantly higher in group 2 than in group 1 patients ($P<0.05$). Although MMP levels in febrile disease controls were significantly higher than those of afebrile controls, the MMP/TIMP ratios of febrile disease controls and afebrile controls were comparable.</p> <p>CONCLUSIONS: These data suggest that patients with Kawasaki disease and high levels of MMP and/or MMP/TIMP are susceptible to coronary arterial lesions. Studies of the effects of MMP inhibitors on coronary outcome may provide evidence that MMP is a viable therapeutic target for the prevention of coronary arterial lesions due to Kawasaki disease.</p>
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<p>CLINICAL OR GROSS VARIANTS</p>	<p>CHARACTERIZATION</p>
<p>CNS</p>	
<p>Kawasaki disease with predominant central nervous system involvement.</p> <p>Tabarki B, Mahdhaoui A, Selmi H, Yacoub M, Essoussi AS.</p> <p>Services de Pediatrie et de Cardiologie, Hopital Farhat-Hached, Sousse, Tunisia.</p>	<p>Pediatr Neurol 2001 Sep;25(3):239-41 Abstract quote</p> <p>A 4-year-old female was hospitalized with clinical and electroencephalographic evidence of acute encephalopathy. Five days later the classic signs of Kawasaki disease appeared.</p> <p>The neurologic outcome in this female was poor despite early treatment with immunoglobulin.</p> <p>Like many other vasculitidies, Kawasaki disease can have predominant neurologic symptoms as the initial presentation and during the subsequent evolution of the condition.</p>

<p>CORONARY ANEURYSMS</p>	
<p>Giant coronary aneurysms due to Kawasaki disease: A case-control study.</p> <p>Nakamura Y, Yashiro M, Oki I, Tanihara S, Ojima T, Yanagawa H.</p> <p>Department of Public Health, Jichi Medical School, Tochigi, Department of Environmental Medicine, Shimane Medical University, Izumo and Saitama Prefectural University, Koshigaya, Japan.</p>	<p>Pediatr Int 2002 Jun;44(3):254-8 Abstract quote</p> <p>Background: Epidemiologic features of giant coronary aneurysm due to Kawasaki disease and its risk factors are still not clear.</p> <p>Methods: Sixty-six patients with giant coronary aneurysms were reported to a 15th nationwide survey of Kawasaki disease in Japan. With all other patients treated in the same hospital as a control group, odds ratios were calculated for certain potential risk factors.</p> <p>Results: Infant males aged less than 1 year, neutrophil concentration among leukocyte, late administration of intravenous gammaglobulin (IVGG) therapy and additional administration of IVGG were considered as risk factors of giant coronary aneurysms due to Kawasaki disease. In univariate analysis, use of IVGG therapy and a large amount of IVGG (2500+ mg/kg) elevated the risk, whereas the relationship disappeared after the adjustment.</p> <p>Conclusions: The observation of 66 cases with giant coronary aneurysms due to Kawasaki disease reported to the nationwide survey provides some risk factors and consideration about the aneurysms.</p>
<p>ADOLESCENTS AND ADULTS</p>	
<p>Kawasaki disease in older children and adolescents.</p> <p>Stockheim JA, Innocentini N, Shulman ST.</p> <p>Department of Pediatrics, Division of Infectious Diseases, Children's Memorial Hospital Center for Kawasaki Disease, Northwestern University Medical School, Chicago, Illinois, USA.</p>	<p>J Pediatr 2000 Aug;137(2):250-2 Abstract quote</p> <p>Features of 28 patients older than 8 years of age with acute Kawasaki disease were reviewed.</p> <p>Observations included a predominance of male patients and white patients, delays in diagnosis of acute Kawasaki disease, presence of additional signs and symptoms, and a substantial incidence of coronary artery abnormalities (21%) including mild transient changes.</p>

<p>SUDDEN INFANT DEATH SYNDROME</p>	
<p>Sudden infant death caused by a ruptured coronary aneurysm during acute phase of atypical Kawasaki disease</p> <p>Emiliano Maresi, MD Rita Passantino, MD Rosalba Midulla, MD Gabriella Ottovoggio, MD Elisabetta Orlando, MD Gaspere Becchina, MD Loredana Meschis, MD Giorgio Amato, MD</p>	<p>Hum Pathol 2002;32:1407-1409. Abstract quote</p> <p>This article describe's a case of atypical Kawasaki disease (AKD) with lack of typical clinical signs and rapid fatal course in a 2-month-old infant, who 1 week before hospitalization demonstrated rhinitis, coughing without fever, and later conjunctival hyperemia and allergic exanthema on chest and arms.</p> <p>On admittance, labwork highlighted the following: leukocytosis, thrombocytosis, elevated sedimentation rate, and positive C-reactive protein. General conditions remained mediocre for 7 days until sudden death occurred. The autopsy confirmed death caused by cardiac tamponade caused by a ruptured inflamed aneurysm of the left anterior descending coronary artery.</p> <p>We believe that the currently accepted clinical diagnostics criteria for KD in infants 2 years of age or younger can cause missed in vita diagnosis of AKD. For such, any typical clinical sign of KD whenever associated with thrombocytosis and elevated indices of phlogosis, should led to suspicion of KD and permit cardiovascular examination, and thus early treatment.</p>

<p>LABORATORY/RADIOLOGIC/OTHER TESTS</p>	<p>CHARACTERIZATION</p>
<p>RADIOLOGY</p>	
<p>ANGIOGRAPHY</p>	
<p>Coronary magnetic resonance angiography in adolescents and young adults with kawasaki disease.</p> <p>Greil GF, Stuber M,</p>	<p>Circulation 2002 Feb 26;105(8):908-11 Abstract quote</p> <p>BACKGROUND: In patients with Kawasaki disease, serial evaluation of the distribution and size of coronary artery aneurysms (CAA) is necessary for risk stratification and therapeutic management. Although transthoracic echocardiography is often sufficient for this purpose</p>

<p>Botnar RM, Kissinger KV, Geva T, Newburger JW, Manning WJ, Powell AJ.</p> <p>Department of Cardiology, Children's Hospital, Boston, Mass 02115, USA.</p>	<p>initially, visualization of the coronary arteries becomes progressively more difficult as children grow. We sought to prospectively compare coronary magnetic resonance angiography (MRA) and x-ray coronary angiography findings in patients with CAA caused by Kawasaki disease.</p> <p>METHODS AND RESULTS: Six subjects (age 10 to 25 years) with known CAA from Kawasaki disease underwent coronary MRA using a free-breathing T2-prepared 3D bright blood segmented k-space gradient echo sequence with navigator gating and tracking. All patients underwent x-ray coronary angiography within a median of 75 days (range, 1 to 359 days) of coronary MRA. There was complete agreement between MRA and x-ray angiography in the detection of CAA (n=11), coronary artery stenoses (n=2), and coronary occlusions (n=2). Excellent agreement was found between the 2 techniques for detection of CAA maximal diameter (mean difference=0.4 +/- 0.6 mm) and length (mean difference=1.4 +/- 1.6 mm). The 2 methods showed very similar results for proximal coronary artery diameter (mean difference=0.2 +/- 0.5 mm) and CAA distance from the ostia (mean difference=0.1 +/- 1.5 mm).</p> <p>CONCLUSION: Free-breathing 3D coronary MRA accurately defines CAA in patients with Kawasaki disease. This technique may provide a non-invasive alternative when transthoracic echocardiography image quality is insufficient, thereby reducing the need for serial x-ray coronary angiography in this patient group.</p>
<p>ECHOCARDIOGRAM</p>	
<p>Long-term follow-up with stress echocardiograms of patients with Kawasaki's disease.</p> <p>Dunning DW, Hussey ME, Riggs T, Bestervelt R, Goerke C.</p> <p>Department of Cardiology, William Beaumont</p>	<p>Cardiology 2002;97(1):43-8 Abstract quote</p> <p>Patients with a history of Kawasaki's disease (KD), particularly those not treated with intravenous gamma-globulin, are at risk of coronary artery aneurysms and later obstruction.</p> <p>Twenty-eight patients with a history of KD (4 had coronary artery aneurysms) were examined with stress echocardiograms. Fourteen patients received gamma-globulin < or =10 days of the onset, 8 patients received gamma-globulin >10 days and 6 received no gamma-</p>

<p>Hospital, Royal Oak, MI 48073, USA.</p>	<p>globulin.</p> <p>The mean age at diagnosis was 7.2 +/- 4.1 years; the median follow-up was 8.0 +/- 7.4 years. All tests were negative. Using a binomial model, a power of 0.80, a sensitivity of each test of 80% and assuming uniform risk, the individual rate of failure to detect was <7%. At least 640 patients in each group would be needed to detect a difference of 3.5% vs. 7.0% and 184 in each group would be needed to detect a difference of 1.5% vs. 7.5%.</p> <p>We conclude that the probability of an abnormal stress echo in asymptomatic patients with a history of KD is at most 7% and that a more precise determination of the risk of an abnormal stress echo in KD requires a much larger study.</p>
<p>PET SCAN</p>	
<p>Positron emission tomography for the assessment of myocardial viability in Kawasaki disease using different therapies.</p> <p>Hwang B, Liu RS, Chu LS, Lee PC, Lu JH, Meng LC.</p> <p>Department of Paediatrics, National Yang-Ming University and Veterans General Hospital, Taipei, Taiwan, Republic of China</p>	<p>Nucl Med Commun 2000 Jul;21(7):631-6 Abstract quote</p> <p>13N-ammonia and 18F-fluorodeoxyglucose positron emission tomography (PET) of the heart were performed on 30 children with a history of Kawasaki disease.</p> <p>The results indicated PET abnormalities in 61.1% of patients during the acute and subacute stages and in 41.2% of patients in the convalescent stage of Kawasaki disease. Two-dimensional echocardiography and coronary angiography could not predict the myocardial viability and perfusion as well as PET. Different therapies during the acute stage of the disease did not effectively prevent myocardial damage, despite the absence of coronary arterial abnormalities.</p> <p>The patients who received 400 mg x kg(-1) x day(-1) of intravenous immunoglobulin (IVIG) for 5 days had a significantly lower incidence of PET abnormalities than those who received a single dose of 2000 mg x kg(-1) IVIG (P < 0.05).</p>
<p>Laboratory Markers</p>	
<p>Elevated ESR</p>	

<p>Elevated acute phase reactants</p>	
<p>Thrombocytosis</p>	<p>Usually not until the subacute phase</p>
<p>Elevated serum levels of matrix metalloproteinase-9 (MMP-9) in Kawasaki disease.</p> <p>Takeshita S, Tokutomi T, Kawase H, Nakatani K, Tsujimoto H, Kawamura Y, Sekine I.</p> <p>Department of Paediatrics, National Defense Medical College, Tokorozawa, Saitama 359-8513, Japan.</p>	<p>Clin Exp Immunol 2001 Aug;125(2):340-4 Abstract quote</p> <p>Matrix metalloproteinases (MMPs) play an important role in the progression of tumour cells and the invasion of inflammatory cells by degrading the extracellular matrix. In the MMP family, MMP-9 gelatinase is thought to contribute to the pathogenesis of inflammatory arteritis by disrupting the elastic lamina.</p> <p>The aim of the present study is to investigate the potential role of MMP-9 in Kawasaki disease (KD), an acute type of systemic vasculitis in children. We studied the total levels of MMP-9 (free proMMP-9 and free MMP-9) in the sera using a new assay system and the expression of MMP-9 mRNA in the leucocytes using reverse transcription-polymerase chain reaction in 18 patients with KD, 10 patients with sepsis and 10 healthy children (HC). The serum MMP-9 levels were significantly higher ($P < 0.01$) in the acute phase of KD than in the acute phase of sepsis and HC. In the time course of KD, the serum MMP-9 levels decreased significantly ($P < 0.01$) from the subacute through the convalescent phases. In the acute phase of KD, the serum MMP-9 levels showed a significantly positive correlation ($P < 0.05$) with the circulating leucocyte counts, especially the neutrophil counts. Furthermore, the expression of MMP-9 mRNA in the circulating leucocytes increased in the acute phase of KD and decreased from the subacute through the convalescent phases.</p> <p>These findings indicate that an excessive amount of MMP-9 is present in the plasma during the acute phase of KD, thus suggesting that circulating leucocytes may be a source of the MMP-9 secreted into the circulation.</p>

<p>PROGNOSIS AND TREATMENT</p>	<p>CHARACTERIZATION</p>
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<p>PROGNOSTIC FACTORS</p>	<p>Dependent upon the intervention with IVIG Coronary artery thrombosis remains the most serious complication, usually occurring within 1-4 weeks after the onset of fever but only occurs in 5-10% of patients if IVIG is started</p>
<p>Mortality among persons with a history of Kawasaki disease in Japan: the fifth look.</p> <p>Nakamura Y, Yanagawa H, Harada K, Kato H, Kawasaki T.</p> <p>Department of Public Health, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Tochigi 329-0498, Japan.</p>	<p>Arch Pediatr Adolesc Med 2002 Feb;156(2):162-5 Abstract quote</p> <p>OBJECTIVE: To determine whether patients with Kawasaki disease have a higher death rate than an age-matched healthy population after disease occurrence.</p> <p>STUDY DESIGN: From July 1, 1982, to December 31, 1992, 52 collaborating hospitals collected data on all patients with a new definite diagnosis of Kawasaki disease. Patients were followed up until December 31, 1999, or death. The expected number of deaths was calculated from Japanese vital statistics data and compared with the observed number.</p> <p>RESULTS: Of 6576 patients enrolled, 27 (19 male, 8 female) died. The standardized mortality ratio (the observed number of deaths divided by the expected number of deaths based on the vital statistics in Japan) was 1.25 (95% confidence interval, 0.84-1.85). Despite the high standardized mortality ratios during the acute disease phase, the mortality rate was not high after the acute phase for the entire group of patients. Although the standardized mortality ratio after the acute phase was 0.76 for those without cardiac sequelae, 6 male patients (no female patients) with cardiac sequelae died during this period, and the standardized mortality ratio for the male group with cardiac sequelae was 2.35 (95% confidence interval, 0.96-5.19).</p> <p>CONCLUSIONS: Although it was not statistically significant, the mortality rate among male patients with cardiac sequelae due to Kawasaki disease seemed higher than that in the general population. On the other hand, mortality rates for female patients with sequelae and both male and female patients without sequelae were not elevated.</p>
<p>RECURRENCE</p>	

Incidence rate of recurrent Kawasaki disease in Japan.

Nakamura Y, Hirose K, Yanagawa H, Kato H, Kawasaki T.

Department of Public Health, Jichi Medical School, Minamikawachi, Japan.

Acta Paediatr 1994 Oct;83(10):1061-4 Abstract quote

To calculate the incidence of recurrent Kawasaki disease and to discuss some potential risk factors for its recurrence, we observed a cohort consisting of those followed-up since the first episode of the disease.

A total of 4560 persons, with 16,500.4 person-years were observed from the second month after the first episode of the disease to the end of 1989. The mean observation period was 3.62 years. The overall incidence rate was 5.21 per 1000 person-years, with a higher incidence within the 2 years from the first episode; although not statistically significant, the incidence was higher among males and those who experienced the first episode at ≤ 2 years of age.

The possibility of i.v. gamma globulin therapy being one of the risk factors was negated by a stratified analysis to control confounding factors but supported by univariate analysis.

A case-control study of recurrent Kawasaki disease using the database of the nationwide surveys in Japan.

Nakamura Y, Yanagawa H.

Department of Public Health, Jichi Medical School, Tochigi, Japan.

Eur J Pediatr 1996 Apr;155(4):303-7 Abstract quote

In spite of many reports of recurrent Kawasaki disease, little information about the risk factors associated with recurrence is available.

We conducted a case-control study on 150 cases of recurrent Kawasaki disease and 1173 pair-matched controls selected from the database of nationwide surveys of the same disease in Japan. Items observed were: sex, age, use of intravenous gamma globulin, and cardiac sequelae at the first episode.

Sex and cardiac sequelae did not affect the risk of recurrence. One- to 2-year-old children were more likely to be affected again than infants (odds ratio [OR] = 1.42; 95% confidence interval [CI], 0.94-2.13), and children who were 3 years of age or older were less likely to experience a recurrence than infants (OR = 0.59; 95% CI, 0.34-1.02). Intravenous gamma globulin therapy at the first episode increased the risk for recurrence of Kawasaki disease within 12 months (OR = 2.66, 95% CI, 1.06-6.66). However, it did not affect recurrences 12 months after the first episode (OR = 1.02; 95% CI, 0.53-1.97).

CONCLUSION: Patients with Kawasaki disease treated

	<p>with intravenous gamma globulin are 2.66 times as likely to be affected by the disease again within 12 months as those treated without intravenous gamma globulin.</p>
<p>Cardiac sequelae in recurrent cases of Kawasaki disease: a comparison between the initial episode of the disease and a recurrence in the same patients.</p> <p>Nakamura Y, Oki I, Tanihara S, Ojima T, Yanagawa H.</p> <p>Department of Public Health, Jichi Medical School, Tochigi, Japan.</p>	<p>Pediatrics 1998 Dec;102(6):E66 Abstract quote</p> <p>OBJECTIVE: Cardiac sequelae develop more frequently after recurrent Kawasaki disease than from the initial onset of the disease. The purpose of this study was to observe the existence of the sequelae at the initial and second onsets of the disease simultaneously with a large cohort.</p> <p>MATERIALS AND METHODS: From the database of patients with Kawasaki disease prepared by the Japanese Kawasaki Disease Research Committee, 559 cases with recurrences recorded between 1989 through 1994 and their initial occurrence listed in the database were selected. Their proportions of cardiac sequelae after the initial and second onsets of Kawasaki disease were compared.</p> <p>RESULTS: Of the 68 patients with cardiac sequelae after the initial onset, 32 (47%) suffered the sequelae after the second onset, whereas 78 (16%) of the 491 who were without cardiac sequelae after the initial onset developed the sequelae after the recurrence. Both proportions were higher than proportions in all patients with Kawasaki disease. In addition to the sex (male) and the existence of the sequelae after the initial onset, age at the second onset (older age) and the interval between the two episodes (longer period) were suspected to be risk factors for sequelae attributable to recurrent Kawasaki disease.</p> <p>CONCLUSION: Linked data of the initial and second episodes of Kawasaki disease showed that the risk of developing cardiac sequelae attributable to recurrent Kawasaki disease is high among both those with and without the sequelae at the initial episode. mucocutaneous lymph node syndrome, recurrence, cardiac sequelae, risk factors.</p>
<p>Incidence rate of recurrent Kawasaki disease and related risk factors: from the results</p>	<p>Acta Paediatr 2001 Jan;90(1):40-4 Abstract quote</p> <p>To investigate the incidence of recurrent Kawasaki disease, and to discuss some of the potential risk factors, data of the 13th and 14th nationwide surveys of Kawasaki</p>

<p>of nationwide surveys of Kawasaki disease in Japan.</p> <p>Hirata S, Nakamura Y, Yanagawa H.</p> <p>Department of Public Health, Jichi Medical School, Tochigi, Japan.</p>	<p>disease in Japan were analyzed.</p> <p>To calculate the rate of recurrence, 10679 patients with 31501.9 person-years were observed. The mean observation period was 2.95 y. The rate of recurrence was 6.89 per 1000 person-years, with a high incidence within the 12 mo following the first episode.</p> <p>CONCLUSION: The incidence was high among those under 3 y of age and those with cardiac sequelae during the first episode. None of the other factors affected the incidence.</p>
<p>TISSUE PLASMINOGEN ACTIVATORS</p>	
<p>Low tissue plasminogen activator relative to plasminogen activator inhibitor-1 as a marker of cardiac complication in children with Kawasaki disease.</p> <p>Sakai M, Asayama K, Otabe T, Kohri T, Shirahata A.</p> <p>Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan.</p>	<p>Clin Appl Thromb Hemost 2001 Jul;7(3):214-8 Abstract quote</p> <p>To determine whether the fibrinolytic system is related to the occurrence of cardiac complication in Kawasaki disease, we measured tissue plasminogen activator, plasminogen activator inhibitor-1, and related factors in the plasma of children with Kawasaki disease. Patients (mean age, 1.8 years) were classified into patients with cardiac complication (n = 9) and no complication (n = 14) groups echocardiographically. They underwent single, high-dose, intravenous-gamma-globulin infusion therapy.</p> <p>Blood was drawn just before and the day after the single high-dose intravenous gamma-globulin infusion therapy (acute phase), and at early and late convalescent phases. Leukocytosis was normalized immediately after the single, high-dose, intravenous gamma-globulin infusion therapy. C-reactive protein and fibrinogen were increased in the acute phase and normalized by convalescent phases. D-dimer fraction of fibrin degradation products changed in a similar manner. Tissue plasminogen activator and plasminogen activator inhibitor-1 were increased in acute phase.</p> <p>The tissue plasminogen activator/plasminogen activator inhibitor-1 ratio was lower in the complication group than in the no complication group throughout the observation period (0.095 versus 0.208 after single, high-dose, intravenous gamma-globulin infusion therapy, p = 0.006; 0.094 versus 0.183 at late convalescent phase, p = 0.024).</p>

	<p>A low tissue plasminogen activator/plasminogen activator inhibitor-1 ratio can predict the propensity for cardiac complication, and can help the physician to decide whether additional therapies are necessary in acute phase Kawasaki disease.</p>
TREATMENT	<p>Curr Opin Pediatr 1998;10:24-33 Intravenous IgG in single infusion of 2 g/kg over 10 hours ASA 80-100 mg/kg/d in 4 divided doses followed by decreased dosage to 3-5 mg/kg/d after the 14th day of illness or at defervescence</p>
ANTI-OXIDANTS	
<p>Antioxidants may mitigate the deterioration of coronary arteritis in patients with Kawasaki disease unresponsive to high-dose intravenous gamma-globulin.</p> <p>Shen CT, Wang NK.</p> <p>Department of Pediatrics, Cathay General Hospital, 280 Jen-Ai- Road, Section 4, Taipei, Taiwan.</p>	<p>Pediatr Cardiol 2001 Sep-Oct;22(5):419-22 Abstract quote</p> <p>During the early stages of Kawasaki disease, a marked increase in oxygen-free-radicals (OFRs), which are produced by activated polymorphonuclear cells, may induce coronary arteritis.</p> <p>Early use of high-dose intravenous gamma-globulin (IVIG) and aspirin effectively blocked this deteriorating course of coronary arteritis; however, late use of IVIG, even using a high-dose schedule, did not achieve the same efficacy. The causes and reactions to the scenario of IVIG refractoriness have rarely been mentioned in the literature.</p> <p>We present an 11-month-old male infant with Kawasaki disease and deteriorating coronary arteritis owing to late use of IVIG who showed dramatic responsiveness to the addition of alpha-tocopherol and ascorbic acid. We also discuss the possible mechanism.</p>
CORTICOSTEROID	
<p>Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy.</p>	<p>Pediatr Int 2001 Jun;43(3):211-7 Abstract quote</p> <p>BACKGROUND: We compared the efficacy and safety of additional intravenous immune globulin (IVIG) therapy with steroid pulse therapy in patients with IVIG-resistant Kawasaki disease.</p> <p>METHODS: Two-hundred and sixty-two consecutive</p>

<p>Hashino K, Ishii M, Iemura M, Akagi T, Kato H.</p> <p>Department of Pediatrics, Kurume University School of Medicine, Kurume, Japan.</p>	<p>patients had been treated with a single dose of IVIG (2 g/kg) and aspirin (30 mg/kg per day). Thirty-five patients (13.4%) were not clinical responders to the initial IVIG treatment. They received an additional IVIG treatment (1 g/kg) within 48 h after the initial treatment. Seventeen patients (6.5%) did not respond to the additional IVIG treatment. We randomly divided these patients into two groups: group 1 consisted of eight patients who were treated with a single additional dose of IVIG (1 g/kg), while group 2 consisted of nine patients who were treated with steroid pulse therapy.</p> <p>RESULTS: The IVIG-resistant patients had a high incidence of coronary artery lesions (CAL; 48.6%). Five patients (62.5%) in group 1 had CAL, including two patients who each had a giant aneurysm and three patients who each had a small aneurysm. Seven patients (77.8%) in group 2 had CAL, including two patients who each had a giant aneurysm, two patients who each had a small coronary aneurysm and three patients who each showed transient dilatation during steroid pulse therapy. There was no significant difference in the incidence of CAL between the two groups. The duration of high fever in group 2 (1.4~0.7 days) was significantly shorter than in group 1 (4.8~3.4 days; P<0.05). The medical costs for the treatment of patients in group 2 (113, 012 yen +/- 22,084) were significantly lower than those for group 1 (144,194 yen +/- 12,914; P<0.05).</p> <p>CONCLUSIONS: Steroid pulse therapy may be useful in the treatment of patients with IVIG-resistant Kawasaki disease who experience prolonged fever. However, transient dilatation of the coronary artery is observed during steroid pulse therapy, so careful echocardiographic examination should be performed for those patients receiving steroid pulse therapy for the sake of early detection of coronary artery abnormalities.</p>
<p>PTCA</p>	
<p>Application of percutaneous transluminal coronary angioplasty to coronary arterial stenosis in Kawasaki disease.</p>	<p>Circulation 1996 May 1;93(9):1709-15 Abstract quote</p> <p>BACKGROUND: Percutaneous transluminal coronary angioplasty (PTCA) has rarely been performed on patients with coronary lesions that result from Kawasaki disease. In this study, we retrospectively evaluated the</p>

<p>Ino T, Akimoto K, Ohkubo M, Nishimoto K, Yabuta K, Takaya J, Yamaguchi H.</p> <p>Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan.</p>	<p>effectiveness of PTCA in five patients with coronary arterial stenosis that resulted from Kawasaki disease and reviewed previous reports for possible indicators of PTCA effectiveness.</p> <p>METHODS AND RESULTS: Five patients, ranging in age from 2 to 16 years (median 8 years) underwent conventional PTCA for localized stenosis. The lesion targeted for PTCA was located in the middle right coronary artery of three patients and in the left anterior descending artery in two patients. In four of the five patients, PTCA was angiographically effective, with stenosis rates improving from 84 +/- 10% to 33 +/- 11% (P<.05). When the previously reported cases of six similar patients were taken into consideration, the only predictor of successful PTCA seemed to be the time elapsed between the onset of Kawasaki disease and performance of this procedure.</p> <p>CONCLUSIONS: In cases in which patients show significant localized stenosis as a result of Kawasaki disease, PTCA should be attempted within 6 to 8 years of the onset of the disease. Additionally, intravascular ultrasound imaging was found to be a useful tool for evaluating internal morphology before and after PTCA. In older patients with coronary calcification, other alternatives to PTCA, such as the use of a rotablator or an atherectomy catheter, should be considered.</p>
<p>SURGERY</p>	
<p>Follow-up study of coronary artery bypass grafting in patients with Kawasaki disease.</p> <p>Inoue T, Otaki M, Oku H, Fukuda T, Shinohara T.</p> <p>Department of Cardiovascular Surgery, Kinki University School of Medicine, Osaka-Sayama, Osaka, Japan.</p>	<p>Am Heart J 2001 Oct;142(4):740-4 Abstract quote</p> <p>BACKGROUND: The purpose of this study was to assess the long-term clinical outcome of coronary artery bypass grafting in pediatric patients with Kawasaki disease.</p> <p>METHODS: Six patients (mean age, 9.3 +/- 1.6 years) underwent coronary artery bypass grafting between September 1985 and December 1992. The number of bypass grafts placed was 1 to 2 per patient (mean 1.3 +/- 0.5). The left internal mammary artery (IMA) was used as a bypass graft in 3 patients, bilateral IMA in 1, and saphenous vein in 3. All patients underwent postoperative evaluations after 1 month and between 5 and 10 years.</p> <p>RESULTS: Follow-up ranged between 9 and 16 years (mean 12.6 +/- 2.7 years). Stress myocardial scintigraphy</p>

	<p>identified 2 patients with transient ischemia, one of whom died suddenly after 16 postoperative years. Coronary angiography demonstrated that the grafts of 5 patients were patent at both the short- and long-term follow-up. However, in 1 patient, the IMA that was grafted to the diagonal artery was occluded 1 month after surgery. Five survivors are in good health, without clinical angina.</p> <p>CONCLUSIONS: We consider that coronary revascularization with bilateral IMA grafts may provide a more favorable prognosis in patients with severe Kawasaki coronary artery disease. Stress myocardial scintigraphy and echocardiography can be used effectively to follow such patients.</p>
<p>Coronary artery bypass grafting in an adult case with Kawasaki disease.</p> <p>Hayashida N, Tayama E, Teshima H, Kawara T, Aoyagi S.</p> <p>Department of Surgery, Kurume University, 67 Asahi-machi, Kurume 830-0011, Japan.</p>	<p>Ann Thorac Cardiovasc Surg 2002 Feb;8(1):47-50 Abstract quote</p> <p>Surgical revascularization for coronary artery lesions secondary to Kawasaki disease has been rarely reported in adult patients.</p> <p>We reported an adult case with few coronary risk factors but with multiple coronary artery aneurysms and obstructive lesions presumably secondary to Kawasaki disease who underwent coronary artery bypass grafting (CABG) with multiple arterial grafts. The postoperative course was uneventful.</p> <p>Because coronary artery sequelae of Kawasaki disease can be a cause of ischemic heart disease even in adults, heightened awareness of this possibility is required for young adults with coronary lesions but without coronary risk factors.</p>
<p>THROMBOLYTIC AGENTS</p>	
<p>Alleviation of myocardial ischemia after Kawasaki disease by heparin and exercise therapy.</p> <p>Tateno S, Terai M, Niwa K, Jibiki T, Hamada H, Yasukawa K, Honda T, Oana S, Kohno Y.</p>	<p>Circulation 2001 May 29;103(21):2591-7 Abstract quote</p> <p>BACKGROUND: Heparin promotes angiogenesis. We evaluated the effects of combined treatment with heparin and exercise on myocardial ischemia in the chronic stage of Kawasaki disease.</p> <p>METHODS AND RESULTS: This study was conducted in 7 patients (aged 6 to 19 years) who had a totally occluded coronary artery and stress-induced myocardial ischemia in</p>

<p>Departments of Pediatrics, Chiba University School of Medicine, Chiba Cardiovascular Center, Chiba, Japan.</p>	<p>the collateral-dependent areas. Twice-daily exercise using a bicycle ergometer was performed with increments of 0.5 W/kg every 3 minutes up to maximal exertion for 10 days. Heparin, which immediately increased circulating hepatocyte growth factor, was given intravenously 10 minutes before each exercise period. Newly developed myocardial infarction, ventricular tachyarrhythmia, anginal attack, or hemorrhagic complication was not observed in any patient. Dipyridamole-loading single photon emission computed tomography documented improved myocardial perfusion in the collateral-dependent areas and a significant reduction in total defect scores in all patients after the completion of 20 sessions (P=0.01). In control patients who did not receive the heparin-exercise therapy, however, stress defect scores remained unchanged (n=1) or increased (n=2) during follow-up. Computerized quantitative coronary angiography provided evidence that the heparin-exercise therapy increased the diameter of the occluded artery to which collaterals terminated (P=0.001) but not that of the reference artery with which collaterals were not connected (P=0.96).</p> <p>CONCLUSIONS: The findings suggest that a series of heparin and exercise treatments over 10 days may have a dramatic effect on the alleviation of myocardial ischemia in collateral-dependent regions. This may be a safe, noninvasive revascularization therapy for patients with coronary artery occlusion in the chronic stage of Kawasaki disease</p>
<p>Adjunctive therapies in the cath lab. Successful thrombolysis using the combination of tissue plasminogen activator and abciximab in an adult with Kawasaki's disease.</p> <p>Chandwaney RH, Stathopoulos T, Sunew J, McPherson D, Davidson CJ.</p> <p>Northwestern University Medical School, Chicago, Illinois, USA.</p>	<p>J Invasive Cardiol 2001 Sep;13(9):651-3 Abstract quote</p> <p>Kawasaki's disease is an acute systemic vasculitic syndrome that primarily affects children. Coronary aneurysms are common vasculitic sequelae of Kawasaki's disease. Intracoronary thrombosis and embolization are potential consequences of coronary aneurysms.</p> <p>We describe our experience of successful thrombolysis using the combination of reduced-dose intravenous tissue plasminogen activator and abciximab as described in the Thrombolysis in Myocardial Infarction 14 trial (TIMI 14) to treat a patient found to have intracoronary thrombus at the site of aneurysm formation due to Kawasaki's disease</p>