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An epidemic of Kawasaki syndrome in Hawaii

A community-wide outbreak of Kawasaki syndrome, apparently the first in the United States, occurred in Hawaii in the first half of 1978. Twenty-seven of the 33 cases were subjected to intensive epidemiologic and microbiologic study. Patients with Kawasaki syndrome, compared to the general population, more often had Japanese ancestry, high-income status, and possibly a history of respiratory infection in the preceding month (44%). Staphylococcus aureus *was not found in high frequency in the patients (15%), and viral cultures and serologic studies, immune electron microscopy, and guinea pig and primate inoculation did not reveal a causative microorganism. Febrile illnesses in guinea pigs inoculated with a skin biopsy specimen could not be further passaged.*

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ALTHOUGH KAWASAKI SYNDROME (mucocutaneous lymph node syndrome)[1,2] is now widely recognized in Europe and the United States, most published reports outside Japan describe single or small numbers of cases. During the months of February-August, 1978, however, an epidemic of Kawasaki syndrome occurred on the island of Oahu. Attack rates rose sevenfold over those of the previous seven years (to 74 per 100,000 children under age 5 per year), and exceeded those in the most affected prefecture of Japan for 1972 to 1974.[4] The 33 cases in this seven-month period in Hawaii appear to be the first documented epidemic of KS which occurred outside of Japan. More recently, epidemics of 23 cases in Rochester, NY[5] and 57 cases in Massachusetts[5] were reported. The Oahu epidemic offered the opportunity for epidemiologic and microbiologic attempts to identify an infectious agent, chemical toxin, allergen, or host factor responsible for this still idiopathic disease.

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METHODS AND RESULTS

Case identification and clinical findings. On the island of Oahu, 64% of pediatric hospitalizations are at Kauikeolani Children's Hospital in Honolulu, and nearly all of Oahu's civilian pediatricians are on the staff. All cases of KS admitted to KCH come to the attention of the authors

Abbreviations used	
KS:	Kawasaki syndrome
KCH	Kauikeolani Children's Hospital
TSS:	toxic shock syndrome

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Three patients were seen as outpatients referred by their private physicians. In March, 1978, a bulletin describing the diagnostic features of KS was circulated to all physicians in the state, and physicians were asked to report new cases to the Hawaii Department of Health. No cases previously unknown to the authors were reported to the Health Department.

Criteria for the diagnosis of KS were those developed by the Research Committee on Mucocutaneous Lymph Node Syndrome[1] and independently by Melish, et al.[3] They include (1) fever, (2) conjunctival injection, (3) mouth changes consisting of erythematous lips, strawberry tongue, or erythema of the oropharynx, (4) acute edema

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and erythema of hands and feet, subacute desquamation, (5) erythematous rash, and (6) cervical lymph node enlargement of at least 1.5 cm diameter.

All patients fulfilled the first five diagnostic criteria; the sixth criterion, significant lymphadenopathy, was present in 37%. The patients were followed by repeated clinical examination for at least six weeks from the time of diagnosis. All were moderately to severely ill; the average duration of fever was 12.4 days (range 5 to 19). One died on the ninth day of illness with acute pancarditis. Associated features encountered in this group of patients were sterile pyuria, 41%; arthralgia, 25%; large joint arthritis with effusion, 15%; aseptic meningitis, 15%; diarrhea, 22%; acute myocarditis, 7%; hepatitis with jaundice, 7%; and gallbladder hydrops, 3%. All but two patients were seen during the first week of illness.

Three patients, including the fatal case, had a history of previous illness resembling KS—5, 5, and 9 months previously. In one instance, the prior illness met the criteria for diagnosis of KS and was documented in a hospital record.

Microbiology.

Bacterial studies. Blood, throat, nasopharyngeal, stool, and urine cultures were taken from 26 patients. Cultures of CSF from six patients and blood and urine cultures from all were negative. Stool cultures yielded no enteric pathogens and no staphylococci. Group A beta-hemolytic streptococci were not found in any nose or throat cultures. Coagulase-positive staphylococci were recovered from nose or throat of four (15%) patients but not from any other site including blood, stool, urine, and vaginal cultures. Antistreptolysin O or streptozyme titers were negative in all 18 sera tested. Blood cultures and urine cultures for *Leptospira* were negative in all 16 patients tested. Paired acute and convalescent sera from seven patients were tested by microagglutination for antibody to 22 *Leptospira* serotypes; all were negative.

Viral studies. No viral agents were recovered from tissue culture studies of 24 stool samples, 24 nasopharyngeal washings, 22 urine samples, and one homogenized skin biopsy from the seventh day of illness in human fetal kidney cells, WI-38 human fibroblasts, or primary monkey kidney cells. Direct cytopathic effect, hemadsorption, and resistance to challenge with ECHO 11 virus after three or more passages were tested. Six specimens in the fourth passage were tested for antigen reacting with patients' convalescent serum by direct fluorescent antibody staining. Paired acute (< 7 days) and three- to four-week convalescent sera from all 27 patients were tested by the Hawaii Department of Health for antibody to multiple common viruses, including the specific respiratory viruses known to be prevalent in the community during February-April, 1978 (Table I). There were no serologic titer rises to the agents tested in the KS patients. Viruses isolated in the general population by the State Health Department Laboratory Sentinel Physician Program during this period included Influenza A/Texas, A/Victoria, A/USSR, B/Hong Kong, parainfluenza 2, and adenovirus.

Table I. Serologic studies in Kawasaki syndrome undetectable or stable acute and convalescent values: 26 paired sera tested

Influenza A/Texas	CF
A/Victoria	CF
A/USSR	CF
B/Hong Kong	CF
Adenovirus	CF
Para-influenza 1	CF
2	CF
3	CF
Respiratory syncytial virus	CF
Corona virus	CF
Mycoplasma pneumoniae	CF
Measles	HAI
Rubella	HI
Varicella	CF
Cytomegalovirus	CF
Herpes simplex	CF
Mumps	CF
Spotted fever group	CF
Typhus fever group	CF
Q fever *(Coxiella burnetti)*	CF
Chlamydia group	CF
Lymphogranuloma venereum	Fluorescent antibody

Eighteen pairs of sera were tested by the Centers for Disease Control, Atlanta, for antibody to *Legionella pneumophilia*, and all were negative. Six pairs of acute and convalescent sera were tested for viral capsid antigen antibody to Epstein-Barr virus by Dr. Robert Chang, Department of Microbiology, University of California School of Medicine, Davis. None showed a rise in VCA titer for Epstein-Barr virus, and all sera but one had titers less than 1:10. Six acute and seven convalescent sera failed to agglutinate sheep erythrocytes at greater than 1:7 dilution.

Impression smears of a skin biopsy taken during the acute illness showed no fluorescent antibody reaction with the patient's convalescent serum; no significant particles were seen by electron microscopy of similar smears.

Electron microscopy revealed no viral or other apparently significant particles in ten pharyngeal washings, ten stools, four acute sera, or four urine specimens. Immune electron microscopy did not demonstrate additional particles or material aggregated by KS convalescent sera. No concentration of particles was revealed by cesium chloride density gradient fractionation.

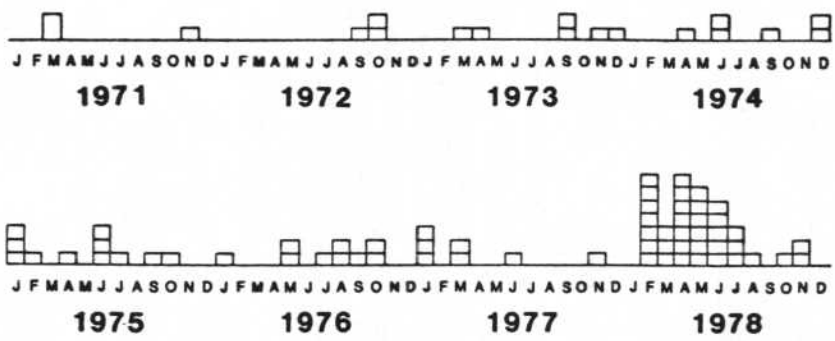

Figure. Monthly occurrence of Kawasaki syndrome on Oahu 1971-1978. Each square represents one case.

Mice were inoculated with eight pharyngeal washings and seven stools, and guinea pigs with 17 acute sera and one whole blood specimen. One guinea pig inoculated with skin biopsy material from an acute case developed a fever and multiple abscesses of the liver. These contained gram-negative anaerobic coccobacilli and staphylococci which did not react more intensely with the original patient's convalescent serum than with the acute serum in indirect fluorescent antibody tests. No disease developed in guinea pigs given intraperitoneal injections of liver suspensions from the first animal. The experiment was repeated with the same results.

Two female 1-year-old Macaca iris monkeys were inoculated intraperitoneally with materials from KS patients. One received 0.8 ml of skin biopsy homogenate and 1.0 ml of whole clotted blood from a patient on the fourth day of illness, and the other received homogenates of heart, spleen, lymph node, and kidney from the patient who died on the ninth day after onset. Observations and body temperature measurements were made daily and a battery of clinical laboratory tests was done biweekly for two weeks, and weekly for the next two weeks. No significant signs of illness or altered laboratory values were noted.

Epidemiology. Detailed epidemiologic studies were performed for 27 of the 28 cases which occurred from February through June, 1978. Epidemiologic interviews were conducted in the home by one of the authors (A. D.). The kitchen, patient's bedroom and play area, and the outdoor areas were inspected for unusual features. The results obtained from interviews with KS patients were compared with the characteristics of the general patient population at KCH, where most of the cases were treated, and with data from the U.S. Census, the Hawaii Health Surveillance Program,[8] and the Hawaii Community Study on Pesticides.[9] The cluster of cases from February to June, 1978, is remarkable against the general background of endemic KS on Oahu (Figure).

Neither the recent epidemic nor the cases prior to 1978 show marked localization in various parts of the island. Dividing Oahu into five areas around population centers and considering only Asian and Hawaiian children under 5 as the denominator, the differences in the incidence in the five areas do not reach statistical significance at the 5% level in the chi square test. The ages of the 13 female and 14 male patients ranged from 3 months to 8 years, with an average of 26 months. All but two patients were less than 3 years of age, the age pattern also typical of endemic cases.

In this epidemic and in our total experience, children of Japanese ancestry are at highest risk and Caucasian children are markedly underrepresented compared to the population on the island of Oahu or to the racial distribution of children seen at Kapiolani-Children's Medical Center. Of the 27 cases encountered from February to June, 1978, 20 were predominantly or completely Japanese, three were Chinese, three were of mixed part-Hawaiian ancestry, and only one was Causcasian, although Oahu's (1975) population was 25% Japanese and 30% Caucasian. The ethnic distribution of the epidemic cases did not differ from that of the endemic cases of the previous seven years. The incidence rates of KS on Oahu from 1971 through the end of this outbreak for Japanese children were 30 per 100,000 under age 5 per year, and for Caucasian children 1.4 per 100,000—a 21-fold difference.

Among the cases of Japanese ancestry seen in February-June, 1978, all but two were of the third and fourth generations in Hawaii. They were culturally very much American in diet and lifestyle. The diet of these children consisted primarily of infant formula and prepared commercial infant foods for the entire first year of life. With the exception that rice is a daily staple, their diet beyond the first year contains little Japanese food. The Japanese-American parents are almost entirely upper-middle class,

Table II. Factors investigated 27 patients with Kawasaki disease Honolulu, Hawaii—1979

1. Sex
2. Physician
3. Parent(s) occupation(s)
4. Both parents working
5. Other family member in school
6. Income
7. Birthplace
8. Household visitor from outside U.S. in past year
9. Travel in Hawaii 1 month prior to illness
10. Travel out of state
11. Birth order of child
12. No other children in family
13. Ethnic background (race)
14. Number of generations in Hawaii if immigrated
15. Immunizations
16. Unusual features of diet
17. Events during pregnancy
18. Infant feeding
19. Housing (age, type, duration of occupancy)
20. Sleeping arrangements
21. Imported toys, clothing, other objects
22. Oriental foods
23. Ajinomoto (monosodium glutamate)
24. Shoyu (soy sauce)
25. Babysitter (day care)
26. Shopping areas
27. Diapers
28. Family medical history
29. Childhood diseases of patient and sibs
30. Animal exposure
31. Occupational chemical exposure of parents
32. Pesticides in house
33. New products in house
34. Detergents used
35. Other illnesses in family around time of patient's illness (1 mo)
36. Previous rash disease (patient)

often professional, and frequently do not speak or understand Japanese, although the grandparents do. Visitors from Japan to the household are very uncommon and, with a few exceptions, contact with the Japanese tourist industry is minimal.

The only Caucasian child in the 1978 outbreak was a boy of 15 months whose parents were from the eastern United States and had resided in Hawaii for only three years. Their life style and diet did not appear to differ significantly from that of other middle-class Caucasian families.

The socioeconomic status of KS families was high, 89% having household incomes over $15,000 and 48% over $30,000. Two to four times more families fell into the higher brackets than would be expected from census estimates. Similar findings using educational status as a socioeconomic indicator were reported in the two outbreaks studied by Bell et al.[5]

Evidence of person-to-person transmission of KS was sought by repeated questions in clinical visits, as well as during the epidemiologic interviews. Two children in one family were affected; the index case was a 24-month-old boy whose 9-month-old sister developed KS seven days after the onset of disease in the index case. The other 25 children had a total of 19 siblings; none of these children or their contacts developed any illness resembling KS. With the exception of the brother-sister pair, the patients had had no contact with each other for at least five months prior to onset of illness and had attended no common events, although parents of three patients knew each other slightly and two affected children were second cousins.

The health histories of the children and their immediate families were given special attention. None of the children had serious congenital malformations or disease, and no family had signs of immunodeficiency or chronic collagen vascular disease. Four of the patients had a history of current or past eczema, hay fever, or asthma. Four other members of 26 immediate families had a history of atopic diseases. No other significant past medical problems were encountered.

Forty-four percent of cases had had a respiratory illness (upper respiratory infection, otitis media, sinusitis) within a month prior to the onset of KS. In 24% of families, a member other than the index case had had a respiratory illness. The expected frequency of respiratory illness among children 0 to 5 years of age was obtained from the Hawaii Health Surveillance program, which conducted interviews of 40,193 persons in Hawaii during 1974-1976 using a modification of the National Health Interview Survey form. The rates for respiratory disease in 0 to 5-year-old children were 23%/month, and for all ages 14%/month. Seasonal variability in the National Health Interview Survey has been at least two-fold and the observed rate therefore cannot be proven to be unusually high. Infection with a particular agent occurring in this frequency, however, would be highly significant. Bell et al[5] have reported antecedent respiratory illnesses in 83 and 56% of patients in the Rochester and Massachusetts epidemics, respectively.

Diarrhea or vomiting in the month prior to onset occurred in 7% of KS patients and 14% of family members. These values exceed the 1%/month expected from the Hawaii Health Program data.

In the month before illness, particularly in the days

immediately preceding referral, eight of the patients had received aspirin and nine had received acetaminophen in usual antipyretic doses. Eighteen of the patients had received antibiotics after onset of fever but before referral; nine had had no antibiotic therapy. No important differences in clinical course, pattern of major manifestations, or duration of fever were noted between those receiving antibiotics and those who were untreated.

Other factors investigated are listed in Table II. None offered etiologic clues as determined by low prevalence of the factor in 27 patients, or by comparison with suitable control information as illustrated above.

DISCUSSION

Until recently, KS has been considered an endemic but not epidemic disease in Japan and in Hawaii. Reports from the mainland United States, Canada, and Europe had generally been of sporadic, widely separated occurrences. Within two years of this epidemic outbreak on the island of Oahu, epidemic occurrences have been documented in Ehime prefecture, Japan (1979), New York City (1978),[6] Rochester, N.Y. (1980), and Massachusetts.[5] All of these outbreaks occurred during the fall, winter, or spring seasons. Endemic KS in Japan shows a slight increase in prevalence in summer months; there is no clear seasonal variation in Hawaii. Despite the temporal clustering of cases, there has been no apparent geographical clustering on Oahu, and no evidence for direct person-to-person spread or common source exposure with the exception of a single apparent sibling-to-sibling transmission.

The ages and clinical features of patients seen within this epidemic period were similar to those with endemic disease, although the nearly equal number of females and males differs slightly from the usual 1.6:1 male predominance.

Our epidemiologic and etiologic studies and those of Bell et al[5] have not revealed the cause of KS. Despite the temporal association of this outbreak with seasonal respiratory illness in the community, no viruses were recovered and no seroconversion to those viruses known to be present in the community was demonstrated. Mild upper respiratory and gastrointestinal illnesses were quite common in the patients and their immediate families in the four weeks prior to onset of illness. However, both types of illnesses are extremely common in the general public and show great variability from month to month and from neighborhood to neighborhood. A prohibitively large prospective study would be necessary to define a "prodromal" illness which several studies now suggest might be associated with KS epidemics.[5]

Because of some close clinical similarities between KS and the newly described toxic shock syndrome, particular attention was paid to the presence of coagulase-positive staphylococci.[10-13] No cases of focal staphylococcal infection were encountered; staphylococcal colonization was found in the nasopharynx or throat in 15% but not in other sites such as stool, vagina, or conjunctiva. Since this is within the range of background colonization, no bacteriologic evidence was found for a relationship of KS to TSS. Comparison of the two syndromes reveals other differences. Hypovolemic shock and azotemia, found in most TSS cases, are not seen in KS. Thrombocytopenia marks the acute phase of TSS, whereas platelets are normal in the acute phase of KS but rise above the normal range in the second and third weeks after onset. Finally, the age group affected by KS is markedly different from that affected by TSS. Kawasaki syndrome affects primarily infants and preschool children with almost no cases over 8 years, whereas TSS primarily affects young menstruating women and to a lesser degree older children and men.

No viruses were recovered using standard tissue culture techniques. Other approaches used to search for novel or difficult to cultivate agents were unrewarding. Animal inoculation did not lead to illness or isolation of a causative agent, except for illness in two guinea pigs which could not be passed to others through inoculation of organ suspensions. Such a pattern of failure to produce illness after the first passage might be produced by a toxin rather than an infectious agent. Other authors have also reported producing illness in guinea pigs which could not be further transmitted by passage of organ suspensions or blood.[14]

The most distinctive feature of KS in Hawaii is its predilection for children of Oriental or Polynesian ancestry rather than Causcasian children. Although Caucasian children have been the majority group affected in two other community-wide outbreaks of KS, these areas have populations which are predominantly Caucasian, with very few Oriental children at risk. In a report on endemic cases reported to the Centers for Disease Control from the entire United States, Oriental children were also overrepresented and Caucasian children were underrepresented.[15] We were unable to determine whether this ethnic predilection for Japanese children is related to a specific genetic susceptibility or to environmental influences. We are currently engaged in studying the distribution of HLA A, B, and D types among patients with KS. In contrast to one report which found a twofold excess of HLA BW22, we and two other groups have not found an excess of any HLA A or B antigen among patients compared to controls. This investigation does indicate that environmental influences are an unlikely explanation for the overrepresentation of Japanese children among KS patients; the majority of patients had a middle-class American life-style.

Careful consideration of the clinical features of this

syndrome, and the absence of cases older than eight years, together with the occurrence of epidemics, strongly suggest that an infectious agent or agents is involved in its pathogenesis. There are suggestions from the urticarial nature of the rash and the pathologic demonstration of vasculitis, arthritis, and carditis appearing in the subacute period, that hypersensitivity or a unique reaction pattern to an inciting agent may be involved. There are hints from our study and from other reports that previous exposure to the agent may have occurred in some cases. The most convincing case for "recurrent disease" was provided by the girl who died; three months previously she had had an illness which fulfilled diagnostic criteria for KS. We suggest that the disease results from an immunologically mediated reaction to an infectious agent which spreads widely through the community. As with poliomyelitis, upper class, "clean," life-styles may influence age at onset or prior immunologic experience, and therefore the rates of clinical KS. This hypothetical undiscovered agent may be a single as yet uncharacterized or difficult-to-cultivate microorganism which can set off this unique reaction pattern just as the β-hemolytic streptococcus incites the poststreptococcal complications of rheumatic fever and glomerulonephritis. Alternately, multiple agents may be able to incite the complete pattern of KS, just as influenza and varicella are associated with Reye syndrome and *Mycoplasma*, streptococci, and drugs are related to the Stevens-Johnson syndrome.

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