Special article

Kawasaki disease

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Summary In this review, I have outlined the clinical picture, epidemiology, pathology, etiology, and current treatment and management of Kawasaki disease. The disease in question has unique features which cannot be classified into any of the categories of conventional pediatric diseases, and thus the elucidation of the etiology and mode of onset may well raise many new medical problems. It is hoped that young practitioners of clinical and fundamental medicine will be able to resolve the problems relating to the disease which remain as quickly as possible.

The daily task of clinicians is to make an accurate diagnosis for each patient seen and to undertake reasonable treatment based on current medical knowledge. It is not sufficient for physicians just to give drugs and to do examinations. Close observation of patients, careful follow-up of the Kawasaki disease clinical course, and the observation of spontaneous cures are all important tasks. This is the starting point of gaining new knowledge in the field of medicine. To perform clinical practice with few errors, accurate observation of patients, and the ability to assess prognosis correctly are required. It is also a fact, however, that, even with all the experience acquired from daily clinical practice, assessment can still be incorrect and patients are still encountered from whom a clinician fails to make a diagnosis. Kawasaki disease was first recognized on the basis of the processes discussed above.

Recognition of Kawasaki disease

I saw the first case of this disease in January 1961, now approximately 30 years ago. The patient had what we now call typical Kawasaki disease, but looking at him from the perspective of that time, I could not form any clear idea of the disease process involved. The clinical chart for this patient was merely filed under GOK (God only knows), with no diagnosis being made. At a case study meeting held during the hospital stay of the patient a doctor asked whether there was any disease other than scarlet fever that caused fever, exanthema, strawberry tongue, swelling of the cervical lymph nodes and desquamation, but I was at a loss to answer. By chance, I happened to encounter a second case and felt that I had actually come across a strange new disease. Thereafter, there were opportunities to see several consecutive cases, and I reported on seven cases of this disease as "a non-scarlet fever febrile desquamative syndrome" in October 1962, at a Chiba district meeting of the Japanese Society of Pediatrics. After this report, as I saw such cases every year, my colleague and I reported in "Allergy" in March 1967, and subsequently received personal communications from many doctors nationwide. It became evident that similar cases were distributed nationwide. Around that time, in January 1967, Matsumi and his colleagues reported on 3 similar cases as "Stevens-Johnson syndrome" at the 183rd Tokyo district meeting. Kusakawa and Minagawa both commented that the cases described did not appear to be Stevens-Johnson syndrome in its exact sense. In April 1967, at the 185th Tokyo district meeting, Yamamoto and Kimura had reported on a case of Stevens-Johnson syndrome complicated with carditis, and they said, in response to comments from Minagawa, that they did not necessarily insist on the term "Stevens-Johnson syndrome" but could not find a more appropriate name. Thus, they clearly experienced the disease in question independently of myself, and noted the complication of carditis as a new finding. Then, immediately after seeing our report appearing in "Allergy", they reported on the "clinical
findings of the acute febrile mucocutaneous lymph node syndrome" at the 187th Tokyo district meeting held in June 1967. In this manner, our report was first noted at a society meeting.

At this meeting, Dr. Fumio Kosaki, the former director of the Department of Pediatrics of the Japanese Red Cross Hospital, proposed that he would like Professor Takatsu to arrange for a panel discussion to further review the disease. Dr. Tadao Takatsu, then Professor of Tokyo University, stated that he had diagnosed the disease as Stevens-Johnson syndrome. Since he had such strong influence in the society, an open forum could not be held for more than 5 years. This is an event which should not be forgotten during the course of the recognition of the disease. Subsequently, discussions took place at a special meeting of clinical pediatric medicine (chairman: Dr. Kenji Hanawa), and Drs. Honma, Mingwa, Matsumi, Yamamoto, and Kawasaki took part in an open forum chaired by Dr. Jushichiro Naito which proved to be very fruitful. This whole episode emphasized that pseudo-academism tends to lack flexibility and tends to be insensitive to "strange things".

In 1979, a research group, sponsored by the Japanese Ministry of Health and Welfare, commenced a comprehensive investigation involving specialists in epidemiology, etiology, pathology and clinical medicine. In 1974, the report made by Shigematsu and his colleagues for "Pediatrics,"2 evoked echoes worldwide, and encouraged investigators in foreign countries (particularly in the United States of America) to study this disease. Kawasaki disease, Kawasaki syndrome, Mucocutaneous Lymph Node Syndrome, is a purely clinical entity which can be diagnosed after recognition and analysis of the 6 principal symptoms as described (Table 1) by the diagnostic guideline for the disease (prepared by the Kawasaki Disease Research Committee of the Ministry of Health and Welfare in 1984). There are no definite laboratory data which might support its diagnosis. In this review, I will discuss in detail the six principal symptoms, the frequency of which is shown in Table 2.

This table was compiled by the Research Committee in October 1971 after detailed examination of individual questionnaires. The examination was conducted by Drs. I. Shigematsu and H. Yanagawa. Hospitals which returned the questionnaires were divided into 2 groups, a group of 16 hospitals which had more than 20 cases each, and a much larger group of 399 hospitals which had seen less than 20 cases each. Of these groups, those seeing over 20 cases each had a total of 389 cases (317 confirmed cases, 72 questionable cases), while the second group had a total of 554 cases (443 confirmed cases, 111 questionable cases). The total was 943 cases. The symptoms can be classified in two categories, principal symptoms and other significant symptoms or findings (refer to Table 2 as reviewed subsequently).

Principal symptoms

Fever of unknown etiology lasting 5 days or more

In general, the onset of the disease is usually with an abrupt and high fever, but without prodromal symptoms such as coughing, sneezing, or rhinorrhea. Lymphadenopathy can sometimes be noticed when the patient complains of neck pain. At times, these symptoms can be seen one day before the abrupt high fever, and wryneck is also seen. There is usually remittent or continuous fever ranging from 38°C to 40°C for 1 to 2 weeks. High fever lasting more than 2 weeks is seen in 14 to 20% of the cases. High fever lasting for 30 days is rarely seen, while high fever lasting any longer may indicate another disease. There is no response to antibiotics or antipyretics. The duration of fever most frequently is 7 to 10 days (Table 1). The mean temperature reached is between 39.0°C and 39.9°C (refer to Table 2).

When fever is prolonged, biphasic and triphasic types predominate (Table 2). According to recent opinion, the longer the fever continues, the higher the possibility of presence of coronary arterial aneurysms.

Bilateral congestion of ocular conjunctivae

Conjunctival injection occurs within 2 to 4 days after the onset of the disease. Upon close examination, each capillary vessel is clear because of individual dilatation. There is no purulent discharge, so the term "conjunctivitis" is not appropriate. There are degrees in the redness of the eyes. In most cases, the redness can be seen at a glance, but in some cases it can be seen only upon close examination. Formation of pseudomembranous, adhesion of the iris, or visual disturbance or damage has never been found. If there is careful slit-lamp examination early in the course of the disease, anterior uveitis can be discovered in rare cases. Conjunctival injection usually subsides within one week, but rarely continues for more than several weeks. This conjunctival injection can be seen in 86.9 to 89.4% of confirmed cases (Table 2).

Changes of the lips and in the oral cavity

Dryness, redness, and fissuring of lips can be seen three to five days after the onset. In some cases, there is bleeding and formation of crust. At a glance, it seems as if there is lipstain on the lips. The membrane of the oral cavity and the pharyngeal mucosa are diffusely red. There is no formation of vesicles, aphtha, or pseudomembranous. Frequently, nonetheless, there is a protuberance of tongue papillae referred to as "straw-
This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. Principal symptoms
1. Fever persisting 5 days or more
2. Changes of peripheral extremities: Initial stage: Reddening of palms and soles, Indurative edema; Convalescent stage: Membranous desquamation from fingertips
3. Polymorphous exanthema
4. Bilateral conjunctival congestion
5. Changes of lips and oral cavity: Reddening of lips, Strawberry tongue, Diffuse injection of oral and pharyngeal mucosa
6. Acute nonpurulent cervical lymphadenopathy

At least five items of 1-6 should be satisfied for diagnosis of Kawasaki disease. However, patients with four items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm is recognized by two-dimensional echocardiography or coronary angiography.

B. Other significant symptoms or findings
1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR, QT intervals, abnormal Q wave, low voltage, ST-T changes, arrhythmias), Chest X-ray findings (cardiomegaly), 2-D echo findings (pericardial effusion, coronary aneurysms), Aneurysm of peripheral arteries other than coronary (axillary etc.), Angina pectoris or Myocardial infarction
2. GI tract: Diarrhea, Vomiting, Abdominal pain, Hydrops of gall bladder, Paralytic ileus, Mild jaundice, Slight increase of serum transaminase
3. Blood: Leukocytosis with shift to the left, Thrombocytosis, Increased ESR, Positive CRP, Hypoalbuminemia, Increased alpha-2-globulin, Slight decrease in erythrocyte and hemoglobin levels
4. Urine: Proteinuria, Increase of leukocytes in urine sediment
5. Skin: Redness and crust at the site of BCG inoculation, Small pustules, Transverse furrows of the finger nails
6. Respiratory: Cough, Rhinorrhea, Abnormal shadow on chest X-ray
7. Joint: Pain, Swelling
8. Neurological: Pleocytosis of mononuclear cells in CSF, Convulsion, Unconsciousness, Facial palsy, Paralysis of the extremities

Remarks:
1. For item 2 under principal symptoms, the convalescent stage is considered important.
2. Male: Female ratio: 1.3-1.5 :1, patients under 5 years of age: 80-85%, fatality rate: 0.3-0.5%
3. Recurrence rate: 2-3%, proportion of sibling cases: 1-2%

Table 1. Diagnostic guideline for Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome) (4th Revised Edition, September 1984; reprinted with the permission of Dr. Tomisaku Kawasaki).

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Table 2. Frequency of principal symptoms in a survey population.

| Principal symptom                  | Group A       | Group B       |
|------------------------------------|---------------|---------------|
|                                    | Confirmed n  | Questionable n | Total      | Confirmed n | Questionable n | Total      |
| Conjunctival congestion            | 269 (89.4)    | 55 (87.3)     | 324        | 359 (86.9)  | 72 (77.4)     | 431        |
| Changes of peripheral extremities  |               |               |            |             |               |            |
| indurative edema                   | 206 (76.6)    | 28 (52.8)     | 234        | 297 (75.0)  | 44 (50.0)     | 341        |
| reddening of palms and soles       | 255 (89.8)    | 43 (79.6)     | 298        | 355 (87.4)  | 61 (70.1)     | 416        |
| membranous desquamation            | 279 (94.3)    | 45 (77.6)     | 324        | 398 (94.3)  | 64 (69.6)     | 462        |
| Changes of lips and oral cavity    |               |               |            |             |               |            |
| strawberry tongue                  | 286 (95.3)    | 45 (80.4)     | 331        | 355 (86.4)  | 77 (81.9)     | 432        |
| reddening of oral mucosa           | 219 (83.3)    | 34 (66.7)     | 253        | 264 (72.1)  | 48 (56.5)     | 312        |
| Exanthema                          | 266 (90.8)    | 46 (83.6)     | 312        | 369 (88.7)  | 83 (83.8)     | 452        |
| Cervical adenopathy                |               |               |            |             |               |            |
| adenopathy                         | 203 (72.0)    | 29 (47.5)     | 232        | 316 (76.3)  | 74 (73.3)     | 390        |
| suppuration                        | 0 (0)         | 0 (0)         | 0          | 8 (2.7)     | 1 (1.5)       | 9          |
| size ≤1.5 cm                       | 103 (59.3)    | 8 (33.3)      | 111        | 179 (58.5)  | 34 (47.9)     | 213        |
| location                           |               |               |            |             |               |            |
| bilateral                          | 60 (34.3)     | 15 (60.0)     | 75         | 142 (47.0)  | 49 (72.1)     | 191        |
| right                              | 66 (37.7)     | 4 (16.0)      | 70         | 85 (28.1)   | 10 (14.7)     | 95         |
| left                               | 49 (28.0)     | 6 (24.0)      | 55         | 75 (24.8)   | 9 (13.2)      | 84         |

cases in Japan (Table 2). Significant swelling is the frequent of the criteria for diagnosis. The swelling usually disappears within defervescence. Of the cases reported by those hospitals seeing less than 20 cases, 8 (2.7%), were said to be suppurative. This opens the possibility to misdiagnosis or secondary infection.

Polymorphous exanthema of torso without vesicles or crusts

Over the 1st to the 5th day after the onset of fever, polymorphous exanthema appears on the torso or the extremities. The nature of the exanthema is polymorphous, being morbilliform, scarlatiniform, and urticariaform and erythema multiform.

In each case, the exanthema is a different combination of these forms. The individual lesions measure 5 to 30 mm in diameter and spread over the torso and extremities within two days. Each lesion becomes increasingly large and often coalescent. They are not accompanied by vesicles or crusts, but sometimes small aseptic pustules are found on the knees, buttocks or other sites of the body. Of the 367 cases hospitalized at our hospital from January 1971 to June 1978, 24 cases (6.5%) showed aseptic small pustules complicated by a skin rash. The site of the small pustules was most often at the knees (9 cases), the buttocks (6 cases), inner thighs (5 cases), forearms, elbows, hands and feet (4 cases each), genital area (3 cases), neck, lower abdominal area and lower legs (2 cases each) and whole body (1 case). Some cases had pustules in more than one site, so the figures above totaled more than 24. Erythema is variable and transient in nature. It changes in appearance according to changes in the fever and other conditions. The rash disappears within one day at the earliest, and may continue for one week at the latest. The frequency of the polymorphous rash is shown in Table 2. Sometimes it is recurrent in nature.

We have observed some cases of an unusual rash. For example, in Japan the multipuncture method is used for BCG inoculation given on the outer and upper left arm. If there is an onset of Kawasaki disease within 4 to 6 months after inoculation, there is fever and a simultaneous rash at the site of the inoculation which has already become a scar. According to our research, from
January 1976 to December 1980, the patients hospitalized at our hospital totaled 419 cases. Among them, there were 295 (70%) cases inoculated for BCG, 86 cases (21%) not inoculated, while unknown cases totaled 38 (9%). The relationship between the period from inoculation to the onset of the disease, and the frequency of the appearance of rash is as follows. Of the 8 cases who contracted the disease within one month of inoculation, 1 case (13%) had a rash at the site of inoculation. Of the 38 cases who had developed the syndrome from one to three months after inoculation, 29 cases (76%) had a rash at the site of the inoculation. Of the 32 cases showing symptoms from four to six months after inoculation, 28 cases (88%) had a rash at the site of inoculation. Of the 39 cases who became ill seven to twelve months after inoculation, 27 cases (59%) had a rash, while, of the 63 cases contracting the disease thirteen to twenty-four months after inoculation, 7 cases (15%) had erythema. Of the 47 cases producing symptoms twenty-five to thirty-six months after inoculation, 7 cases (15%) had erythema. Finally, of the 54 cases who had Kawasaki disease more than thirty-six months after inoculation, no cases had erythema. Why this phenomenon occurs has yet to be clarified.

Changes of the arms and legs

Approximately two to five days after the onset of the disease, when polymorphous exanthema of the torso has appeared, there is reddening of palms and soles, at which time indurative edema also occurs. The degree of swelling is sometimes great, and the skin is shiny and appears to be about to burst. Sometimes, when there is no swelling, there is swelling of the hands and feet a few days after the reddening of the palms and soles has disappeared. After the fever resolves, the swelling also disappears in most cases. From 10 to 15 days after the onset, there is desquamation and fissuring between the nails and the tips of the fingers, after which membranous desquamation spreads over the palm up to the wrist. For the toes, membranous desquamation occurs several days after the appearance of desquamation of the fingers. Membranous desquamation spreads over the soles up to the ankles.

There are cases that have desquamation of the fingertips. There are some atypical cases where there is desquamation of the fingertips but not of the toes. In rare cases, no desquamation occurs. From a month and a half to two months after the onset of the illness, transverse furrows frequently appear in the nails of both the fingers and toes. Some cases have the 5 principal symptoms, but no red palms or indurative edema in the initial stage. If the fingertips are observed carefully in the stage of convalescence, desquamation at the fingertips can be seen in most cases. Fingertip desquamation is one of the most important features of this disease. The frequency of each symptom is shown in Table 2.

Other significant symptoms or findings

Of the other significant symptoms or findings, cardiovascular changes are important, but these will be discussed elsewhere in this issue, so I will not discuss them here. Diarrhea can be seen in about 35% of the patients. Patients with dilatation of the gall bladder often suffer severe abdominal pain, especially in the upper right quadrant of the abdomen. Albuminuria is frequently seen in the acute stage, accompanying aseptic microscopic pyuria. Such aseptic pyuria is caused not only by urethritis, but also by the organs of the upper urinary tract. Almost all of this microscopic pyuria, nonetheless, disappears in the stage of convalescence.

In almost all cases, acute phase reactants (such as leukocytosis with a shift to the left, increased erythrocyte sedimentation rate, positive CRP and so on) can be detected. In general, ASO does not increase. The count of thrombocytes increases from the second week of the illness and, sometimes, reaches 1 to 1.5 million.

Arthralgia or arthritis can be seen in about 25% of cases, depending on the reporting researcher. Figures for aseptic meningitis are also different depending on the researcher, but can be seen in 20 to 50% of cases. According to cytological study, aseptic meningitis if compared to mumps meningitis, shows higher frequencies of macrophages, ependymal cells, and cells of the pia arachnoid. This cause of preocytosis may be due to vasculitis of the small vessels in the meninges. Aseptic meningitis in Kawasaki disease has been reported to be as high as 20 to 50%.

Mild jaundice occurs in about 5% of cases. The total level of bilirubin in serum is always lower than 10 mg/dl. In the acute phase, serum transaminase often increases. GOT and GPT increase from 60 to 200 IU, and LDH increases from 600 to 900 IU. Sometimes there are reports of unusual cases which show the complications ileus, DIC, and problems of the central nervous system such as facial palsy, hemiplegia, encephalopathy, and so on.

Diagnosis

A definite diagnosis of the disease can be made when 5 of the 6 principal symptoms are recognized. If only 4 major symptoms are seen, the diagnosis can be made by detecting coronary arterial aneurysms by echocardiography or angiography. These are described in detail in "Diagnostic Guideline of Kawasaki Disease" (4th revised edition in 1984) (Table 1). Patients with 3 or less principal symptoms who are found to have coronary arterial aneurysms may also exist. In particu-
lar, a patient who has a fever of unknown etiology, persisting for some time, and who shows desquamation from the fingertips but not clear other major symptoms should be suspected of the disease, and should be examined by echocardiography for coronary arterial lesions. If an aneurysm is found, the patient should be regarded as having the "incomplete type" of the disease and treated in a similar manner to those with the full-flow condition. If such a lesion is overlooked, it may result in sudden death.

Reference symptoms
With regard to the important cardiovascular lesions, it can be assumed that, at the acute stage of the disease, carditis and coronary arteritis will develop frequently, although in varying degrees of severity. Accordingly, patients should be admitted to hospital whenever possible, and the progress of the cardiovascular lesions should be carefully monitored by auscultation, chest radiography, electrocardiography and echocardiography.

Echocardiography is particularly important. Extended lesions being to appear at 7-10 days after the onset of the disease, and are detected in 40-45% of patients by 1 month after the onset. These lesions have already begun to regress in about half of the patients at that time. The incidence of extensive lesions at 1 month, 2 months, and 1 year after onset is 20%, 10%, and 5%, respectively. Thus over the course of the disease, the lesions tend to regress, although this process is dependent on the size of aneurysms. Small aneurysms (less than 4 mm in diameter) will regress spontaneously in almost all patients, while medium-sized lesions (4-8 mm in diameter) regress in many cases. Large-sized aneurysms (more than 8 mm in diameter), in contrast, do not usually show spontaneous regression, and may progress to produce eventual stenosis and vascular obstruction in many cases. Patients who have extensive lesions should be followed up by echocardiography while being given anticoagulants. If necessary, arteriography should be performed. When adequate anticoagulation is provided, the progress of occlusive lesions slows down, allowing time for collateral circulation to develop, so that a patient can remain asymptomatic even after complete occlusion of one or more coronary arteries.

The development of collateral circulation is more prominent in younger children, and asymptomatic cases with extensive occlusions are seen only among children. Recently, bypass surgery using the internal mammary artery instead of the saphenous vein has been performed in patients with coronary arterial occlusion due to Kawasaki disease. The long-term patency rate of the grafts has improved, which inspires hope for these patients.

As mentioned above, in Kawasaki disease the cardio-vascular lesions are frequent in the early stages, and therefore, following diagnosis, patients should be admitted to a suitable hospital for adequate treatment and management. If treated as outpatients, such patients should be examined with echocardiography performed by a reliable physician twice or more to check for acute coronary arterial lesions. If extensive lesions are recognized, the management of such a patient should be put in the hands of a specialist with experience in caring for such children.

Epidemiological survey
The research group that the Ministry of Health and Welfare formed in 1970 has conducted a nationwide survey at about two-yearly intervals since the first (led by Drs. Itsuzo Shigematsu and Hiroshi Yanagawa). The survey had been carried out 10 times as of the end of December 1988, with the total number of patients studied amounting to 94,330 (Table 2). During this time, three nationwide epidemics occurred at intervals of 3 to 4 years, in the first halves of 1979 and 1982, and from November 1985 to May 1986.

According to these epidemiological surveys, the age distribution of the disease was a curve with its peak at 1 year of age. Children 4 years old or less were found to account for 80 to 85% of the total number of patients; the sex ratio was 1.3 to 1.5:1 in favor of boys; and the fatality rate decreased from 1 to 2% for the early cases to 0.1% in recent years.

A survey undertaken in Hawaii showed a high morbidity rate among children of Japanese ancestry and, when combined with results obtained on the American continent, the morbidity was shown to be highest for Asian followed by those of African descent, and was lowest for Caucasians. Although the disease has been reported to occur on all continents, it is overwhelmingly more frequent in the more advanced countries and is found less often in developing countries. This suggests that Kawasaki disease is related to the socioeconomic environment.

Pathological features
The pathological features of Kawasaki disease were first reported in detail by Tanaka et al in 1974, while in 1977, Hamashima presented a comprehensive survey of pathological findings at a meeting of the Japanese Society of Pathology. Fujiwara and his colleagues summarized a series of these studies to produce a clinico-pathological picture of Kawasaki disease. Thus the disease frequently develops in infants, and is an acute systemic inflammatory disease characterized by systemic vasculitis which becomes chronic about one
and a half months after onset. No recurrence occurs.

Inflammation of medium-sized vessels initially occurs in both intima and tunica adventitia, and extends to the tunica media in Stage II (weeks 2-4 of the disease). In particular, the coronary arteries are affected by panarteritis and aneurysms develop. Inflammation of small-sized and minute vessels is extensive in Stage I (weeks 1-2 of the disease), but tends to regress in Stage II and III (weeks 4-7 of the disease). Severe stenotic lesions are occasionally found. Fibrinoid necrosis is frequent.

The historical picture of the disease is characterized by edema and cellular infiltration (mainly involving neutrophils and lymphocytes) in Stage I. Severe necrosis, edema, and cellular infiltration (mainly composed of monocytes) is seen in Stage II, in which capillaries and fibroblasts begin to proliferate. So-called granulation tissue is observed in Stage III, while Stage IV is characterized by scar formation.

The major pathological feature of Kawasaki disease is large aneurysms of the major coronary arteries, which particularly tend to develop at their origins. Such aneurysms are observed in 90% of fatal cases. The causes of death are arrhythmia due to myocarditis in Stage I, ischemic heart disease (mainly thrombotic obstruction resulting from coronary aneurysms) in Stage II and III, and cardiac insufficiency or arrhythmias associated with ischemic heart disease or the after effects of myocarditis in Stage IV. A study of patients dying from Kawasaki disease has revealed that 75% of deaths between 1961 and 1967 occurred during the acute stage (Phase I to III), while, in deaths between 1980 and 1983, only 10% were in the acute stage whereas 90% occurred in the stage of convalescence. These changes appear to be attributable to improvements in treatment (such as the use of anticoagulation), and to more careful management.

Etiology and mode of manifestation

Up to now, many hypotheses have been proposed regarding the etiology of the disease, but nothing definitive has been established. There are theories not involving infection, including the theory invoking allergy to synthetic detergent, that suggesting antigenicity to mites, and that suggesting allergy to mercury.

Theories involving infection have proposed rickettsia, various bacteria, candida albicans, and various viruses as the causative agents.

Among these, the theory involving retroviruses proposed in 1986 by doctors of three children's hospitals in the United States of America (Boston, Chicago, and Honolulu) has attracted attention. This hypothesis was almost accepted by many researchers. A cooperative study conducted by the Kawasaki Disease Research Group of the Ministry of Health and Welfare in cooperation with leading Japanese institutions, including the Institute of Virology at Kyoto University, the Institute of Microbiology at Osaka University, and the Department of Virology of the National Cancer Center, however, showed negative results. Thus the etiological investigations of this disease appear to be back where they started.

Various immunological abnormalities have been reported to be associated with Kawasaki disease, but no consistent results have yet been obtained. Thus, the true profile of immunological changes associated with the disease remains unclear. Further progress in areas of medical science, such as etiological microbiology, immunology, and genetics, should eventually clarify the etiology and mode of manifestation of Kawasaki disease.

Current treatment and management

Kawasaki disease is commonly treated by means of antiinflammatory and antithrombotic agents, in particular aspirin. In 1983, Furusho et al. reported the excellent efficacy of high-doses of gammaglobulin for treatment of Kawasaki disease, a treatment shown by Imbach et al to be effective for idiopathic thrombocytopenic purpura. In January 1984, Newburger heard a report by Furusho at the first Japan-US Kawasaki disease workshop held in Hawaii, and soon organized a multicenter cooperative study involving 6 pediatric hospitals with an NIH grant of two million dollars (one dollar/250 yen at that time). The results obtained were presented in August 1986. This report concluded that gammaglobulin was a safe and effective treatment, and should, therefore, be recommended for all patients with Kawasaki diseases until fundamental studies found a better method of treatment.

Subsequent randomized prospective controlled studies showed that use of gammaglobulin given in high dose, gave better results than aspirin used in isolation for treatment. Nevertheless, within the group treated with the gammaglobulin, there were sometimes cases reported with giant aneurysms of the coronary arteries even though treatment had been started in the early stages.

In the same issue, Feigin et al. commented on the report of Newburger et al. saying that "The authors proposed IVGG for all patients, but before using this treatment as routine some additional similar studies should be required. It should be noted that coronary aneurysm is not detected in about 80% of patients. IVGG treatment is very expensive, and therefore before using this type of treatment routinely, clinicians should..."
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