DEFINING A DISEASE

Researchers are still trying to figure out the cause and treatment of Kawasaki syndrome

By JOANNE SILBERNER

In 1972, Marian Melish, a specialist in infectious disease, and Raquel Hicks, a rheumatologist, saw a handful of children with a peculiar set of symptoms: unexplained fever, red eyes, reddened or cracked lips or tongue, reddened and peeling hands or feet, rash and enlarged lymph nodes.

"By three or four cases we knew we were dealing with the same disease," says Melish. "We just didn't know what disease it was."

Both doctors were at the University of Hawaii in Honolulu, fresh from completing their medical training. "We were fairly young and you don't usually think you're going to find a new disease — you think you're seeing something you may not recognize," says Melish.

By 1973, they had seen nine cases and they knew they were on to something. They presented the cases at a pediatric research meeting in May 1974. Soon afterward, a Japanese pediatrician happened to visit the hospital. He had with him pictures of children with a syndrome that was already recognized in Japan; he was trying to determine whether it occurred in other places as well. No one in hospitals across the United States had recognized the disease, but it was very familiar to Melish and Hicks.

"We said not only had we seen it, we have one in the hospital right now," Melish recalls.

The Japanese pediatrician told them about the work of Tomisaku Kawasaki, now at the Japanese Red Cross Medical Center in Tokyo. Kawasaki had first seen a child with the disease in 1961 and soon established the symptoms. The prevalence seemed to be increasing. It primarily hit children under 5, and in addition to the fever, rash and other symptoms, the disease was found to damage arteries and in a handful of instances to result in death.

What the researchers were all seeing is now known as Kawasaki syndrome, and was the subject of a symposium last month in New York at the Second World Congress on Pediatric Cardiology. The conference drew presenters from Japan, the United States and Canada.

What is now known about the disease is that it is rare and that the vast majority of its victims recover. In Japan, where Kawasaki syndrome is most prevalent, 20 of every 100,000 children get it each year. Research on the disease exemplifies medical science in action: Though the cause remains unknown, researchers are stalking a bacterial candidate; clinicians are refining treatment to prevent arterial damage; epidemiologists are showing that the disease comes and goes in cycles. Checks of hospital records reveal that the syndrome may not even be new—it may have lurked, unnoticed, for decades before its discovery.

Kawasaki's first case, in 1961, was a 4-year-old boy. "But at the time I did not diagnose this case; I had to put it in the 'nobody knows' file," he recalled at the New York conference. He saw another six cases in 1962, reported on them at a local pediatric meeting and published his first paper on the syndrome in a Japanese journal in 1967.

Since the discovery, researchers have found that the disease's most damaging and least evident target is the heart, specifically the coronary arteries that branch off from the aorta and feed blood to the heart muscle itself. About 15 to 20 percent of affected children develop aneurysms — ballooning blood vessel walls—in a coronary artery. Most children with aneurysms show no outward signs; it's only by doing sound wave or X-ray studies that the wall weakenings can be seen.

Children who have had aneurysms do not seem to fare as well later on as other Kawasaki victims. "If you've had one, even with regression, there's a suspicion the vessel is not truly normal," says Jane Newburger of Harvard University. During the aneurysm healing process, the inner layer of the blood vessel thickens. Notes Masato Takahashi of the University of Southern California in Los Angeles, "After an aneurysm heals you're not dealing with a completely normal vessel." And whether these children are more susceptible to atherosclerosis remains to be seen.

An aneurysm in the coronary artery can cause narrowing, leaving the artery more prone to blockage and a subsequent heart attack. In addition, the aneurysm changes the fluid dynamics, slowing the blood and making clotting more likely.

This clot-inducing tendency of aneurysms is abetted by blood changes induced by the disease. "During the early recovery phase, the patient's blood is extremely sticky," says Takahashi. "It tends to clot quite easily because platelets [clotting agents] are increased in number and aggregate more easily."

And in the coronary artery, blocking blood flow to part of the heart muscle can mean a heart attack, the primary cause of death in the 0.3 to 2 percent of Kawasaki syndrome patients who die during the acute phase of the disease. Bypass surgery is done on some young children to avoid the damaged vessel.

For most, however, surgery is not necessary. "As we follow patients, a surprising number of them undergo a gradual decrease in size of the aneurysm," says Takahashi. "Within about 30 months, about 80 percent of aneurysms disappear." These children are expected to lead a normal life, he says.

While Kawasaki's first case is now 25 and healthy, few children have been followed for any amount of time. Newburger tells the parents of her aneurysm-free patients that the children have "every reason to expect full and normal lives."

"For our own good, we want to follow them at intervals to prove the theory is correct," says Newburger.

Aspirin, which reduces the blood's clotting tendency, is used to treat Kawasaki syndrome. Early treatment is important, Takahashi notes, because the coronary arteries can be damaged early in the course of the disease.

After the Japanese reported success using gamma globulin, a blood protein that affects the immune system, a multicenter U.S. trial was begun. At the New York meeting preliminary results were reported on 26 children given aspirin and 27 given aspirin plus gamma globulin. After six to seven weeks, four of the children on aspirin alone had aneurysms, compared with only one of the children receiving aspirin plus gamma globulin.

"It's very promising," says Newburger, who is helping to conduct the trial. "But the numbers are still too small to prove it's effective."

While Kawasaki was the first to recognize the syndrome, it may not necessarily be a new entity. Richard Rowe, a pediatric cardiologist at the Hospital for Sick Children in Toronto, says records from his hospital show that a patient was seen there in 1935 whose symptoms match those of the disease. Researchers at other hospitals have found the same evidence of previous, unrecognized instances of Kawasaki syndrome. But curiously, says Kawasaki, in Japan "we cannot find such a case" from decades ago.

One reason the syndrome may not have been recognized until recently, suggests Melish, is that the rash can look a lot like measles. "And until 1970," she says, "there was a lot of measles." In addition, says Melish, the syndrome is becoming more common.

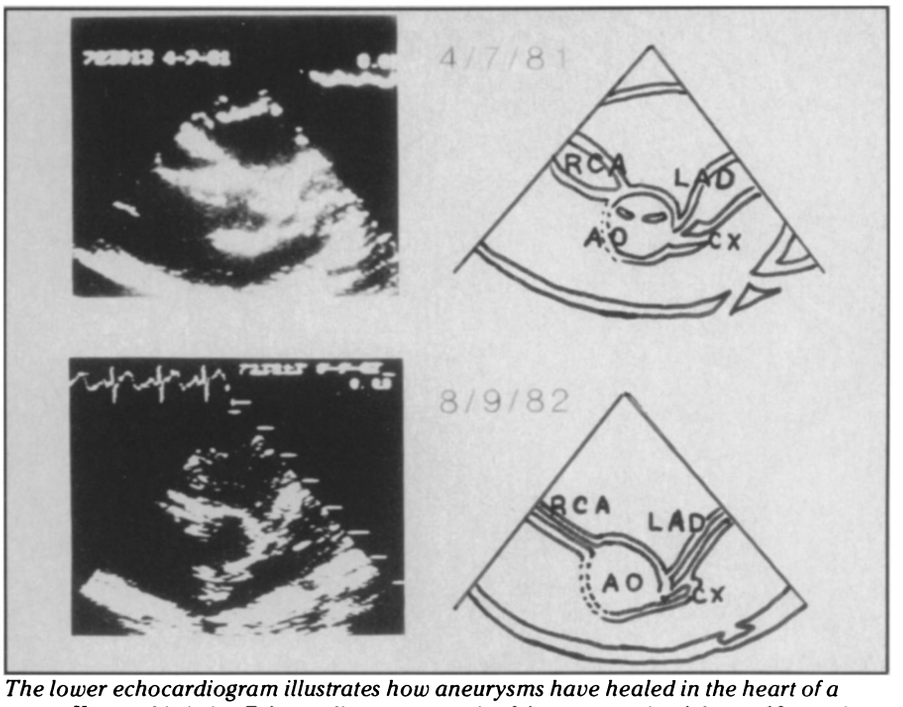
One of the first things that need to be defined in a newly recognized disease is the epidemiology — what populations it strikes, and with what frequency. A worldwide effort sponsored by the International Society of Federation of Cardiology has found the syndrome around the world, with Japan by far predominating — 29,700 cases between 1979 and 1982. Because in essentially every country but Japan the disease is underrecognized and underreported, it is difficult to gauge the international incidence.

The disease itself runs a very similar course in different countries, Rowe notes. There is a lower death rate in Japan — 0.3 percent compared with up to 2 percent elsewhere. One suggestion is that, because of its high prevalence in Japan, the disease tends to be recognized and treated early.

U.S. studies have shown Japanese-Americans to be more vulnerable than other groups. Says Takahashi, who has studied the incidence in Los Angeles, "There's definite evidence for ethnic difference in susceptibility. Japanese children appear to be 10 times as susceptible to this disease as [Caucasian] children."

According to Japanese researchers, the incidence rate in Japan — which is increasing — is usually about 20 per 100,000 children under the age of 9; in epidemics this can go up to 50 or 60. In 1982 the incidence rate reached 72 per 100,000.

According to a report from the Centers for Disease Control (CDC) in Atlanta, between Aug. 22, 1984 and Jan. 6, 1985 there were outbreaks in 10 states and the District of Columbia, affecting 187 children with an additional 75 suspected cases. Since then, says Alan Rauch, a medical epidemiologist at the CDC who has been following the syndrome, two more states have reported outbreaks. But because the CDC depends on voluntary reporting, their data understate actual incidence of the disease.



Takahashi

The lower echocardiogram illustrates how aneurysms have healed in the heart of a young Kawasaki victim. Echocardiogram at top is of the same patient's heart, 16 months earlier. Corresponding diagrams depict aorta (AO), right (RCA) and left (LAD) coronary arteries and circumflex branch (CX).

Kawasaki syndrome tends to hit an area about every third year. Los Angeles had outbreaks in 1980 and 1983. Though Japan had epidemics in 1979 and 1982, so far this year, says one Japanese researcher, the usual incidence has prevailed.

But despite inroads into the epidemiology, the syndrome's cause and method of transmission have remained remarkably resistant to analysis. Not for lack of suggestions.

"Bacteria, fungus, rickettsia [a bacterial form with some virus properties], toxins, even house dust mites have been considered," says Takahashi. "Many things have been proposed, but none has stood the test of time."

Says Rauch, "It is unusual to have an illness around this long for which we don't know the cause. I suspect it probably will end up being something a little bit unusual."

At the cardiology meeting last month, Hirohisa Kato of the Kurume University School of Medicine described the latest bacterial candidate — propioni bacterium acne, which he has found in lymph nodes removed from children with Kawasaki syndrome. Bacteria usually appear after one week in culture, but the p. acne didn't show until the third and fourth week. "That's very unusual," Kato says.

When he put these bacteria into a guinea pig, it lost some fur and had heart problems — a response similar to the dermatological and cardiac effects in humans. When he added blood serum from a child who had recovered from Kawasaki syndrome, which presumably had antibodies to the infectious agent, the effect disappeared. The bacterium is a member of a family that normally lives on human skin; it could thus be merely a contaminant of the lymph node culture.

Kato has isolated a protein produced by these bacteria that he believes may cause the syndrome. But, he notes, "my hypothesis is still controversial. The results have not yet been confirmed by others."

Says Kawasaki, "I think it needs more investigation."

Melish at the University of Hawaii believes the culprit is commonly found in the environment. "Our theory is that it's caused by a common infectious agent that goes through the community every two to three years, infecting a large number of children and causing Kawasaki syndrome in a small minority who are perhaps genetically sensitive."

Transmission doesn't seem to be a factor in epidemic years, since the disease rarely occurs even within the same family. "You might get one child in a neighborhood, and another a few blocks away when there's been no direct contact," says Melish. This suggests an infectious agent that does little or no damage to most children, she notes.

Finding the cause may one day explain some peculiarities of the syndrome. What, for instance, makes Japanese children more vulnerable? What accounts for the two- to three-year cycle and winter-spring prevalence? Are more children getting the syndrome, or is it just being noticed more? And what will happen to these children as they get older? □