Abstract: Although an infectious etiology is strongly suspected in Kawasaki disease (KD), an etiologic agent has not yet been identified. By reviewing epidemiologic data published in past decades, this work highlights a higher incidence of KD when populations were exposed to the risk of Yersinia pseudotuberculosis infection. This hitherto unnoticed element reinforces the hypothesis whereby this bacterium might contribute to the development of KD in some cases.

Key Words: Kawasaki disease, Yersinia pseudotuberculosis, epidemiology

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Kawasaki disease (KD) is an acute multisystem vasculitis of young children and is the leading cause of acquired heart disease in children living in industrialized countries. Despite the fact that illness’s clinical and biologic features (including some immunologic characteristics of superantigen-induced disease) fit well with an infectious etiology, a causative agent has not yet been identified. Yersinia pseudotuberculosis (a Gram-negative enteroinvasive bacillus of the Enterobacteriaceae family) is typically responsible for terminal ileitis and mesenteric lymphadenitis, although some cases can feature a scarlet-fever-like syndrome with conjunctivitis, strawberry tongue, scarlatinoid rash, edema and desquamation, resembling the clinical picture of KD. This severe form of Y. pseudotuberculosis infection, known in Japan since the late 1920s as Izumi fever, was also identified in Far East Russia (where it is called Far East scarlet-fever-like disease) in 1959–1960.

In the early 1980s, Sato et al noted that of 12 hospitalized children with a stool culture positive for Y. pseudotuberculosis, 2 fulfilled the strict clinical criteria of KD. After additional observation, those authors further reported that 57 (35%) of 164 Y. pseudotuberculosis-infected children had KD. In another Japanese study, this diagnosis was made in 29 (12.1%) of 329 patients infected by Y. pseudotuberculosis. Additionally, cardiac alterations, coronary artery dilatations and aneurysms have been observed in children with Y. pseudotuberculosis infection. Lastly, during the 1990s when the idea that a superantigen might contribute to KD first emerged, production of an exotoxin with superantigenic activity (termed YPM, for Y. pseudotuberculosis-derived mitogen) was detected in a Y. pseudotuberculosis strain recovered from the stools of a KD patient. Not all members of this bacterial species synthesize YPM, and interestingly, the genome of an isolate from a patient who developed Far East scarlet-fever-like disease has recently been sequenced; in silico analysis revealed that it contains the YPM-encoding gene (personal data).

Thus a number of clinical and biologic arguments suggest that Y. pseudotuberculosis infection could play a role in KD pathogenesis. This hypothesis implies that epidemiology of both conditions fit together well enough in real populations to support such an association. To investigate whether or not space and time distributions of Y. pseudotuberculosis infection and KD are consistent with an etiologic hypothesis, we compared epidemiologic data for both illnesses published in past decades.

EPIDEMIOLOGIC OBSERVATIONS

Population Distribution. Human pseudotuberculosis has been primarily observed in the northern hemisphere. It is especially prevalent in the Far East with many outbreaks occurring in Japan. To date, Finland is the only other country in the world where several human epidemics have been reported so far. KD is most frequent in Japan with about 170,000 cases registered during the past 4 decades, and many of these cases were epidemic. KD outbreaks have also been reported in Korea as well as in non-Asian countries, such as the United States and Finland.

Age and sex distribution profiles tend to be similar in both pathologies. KD predominantly affects children less than 5 years (85% of all cases), with a men-to-women ratio of about 1.7:1. Y. pseudotuberculosis infection in Japan mainly involves younger age groups (with a peak incidence age of about 2 years) and men (with a men-to-women ratio of about 1.6:1).

Secular Association. In Japan, 3 nationwide outbreaks of KD were observed between 1979 and 1986. After 1986, the overall incidence of KD increased in the Japanese population.
but a nationwide outbreak has not been registered. It is noteworthy that during the period of nationwide KD epidemics, 10 Y. pseudotuberculosis infection outbreaks were recorded in Japan, whereas only 2 occurred during the subsequent 2 decades (Fig. 1).

The only KD outbreak reported to date outside Asia and the United States occurred in Finland during the winter of 1981–1982 in all areas of the country. Strikingly, it was concomitant with the country’s first extensive outbreak of Y. pseudotuberculosis infection. Since then, the incidence of KD has slowly increased, and many widespread pseudotuberculosis epidemics have been registered.

Seasonal Association. Seasonality is a strong epidemiologic characteristic of KD. With the exception of 2 summer outbreaks, all epidemics have peaked between the months of October and May in Japan, Korea and the United States. In these countries, sporadic cases of KD also increase markedly during winter and spring. Although a second disease peak is observed in June–July in Japan and Korea, all Asian and American series show a consistent decrease in the number of cases during the autumn, with a trough in September–October.

In Japan, human infection by Y. pseudotuberculosis is also most common in winter and spring. Of the 12 Japanese outbreaks, 4 and 8 occurred in October–December and in February–June, respectively. Furthermore, individual epidemiologic information is available for 2 Japanese series of sporadic cases (with 23 and 164 cases respectively); both showed the same seasonal distribution—essentially from November to June (93.6% of total cases) with a winter peak in January and a spring peak in April–May. The seasonal distribution of cases of both sporadic and epidemic Y. pseudotuberculosis infection in humans is consistent with the documented presence of the bacterium in the environment. A 1-year survey of fresh water from 40 rivers in Japan revealed that Y. pseudotuberculosis could only be isolated from November (51.7% of the rivers) to May (17.5%). Similar results were found in a survey of 1712 wild micromammals in which Y. pseudotuberculosis was recovered only from November to June, with a peak in December–February.

In Finland, the winter-spring increase of KD is less pronounced than in other countries and the seasonal pattern is different. The national registration data (initiated in 1982 and discontinued in 1992) do not show a significant decrease in the incidence of KD during the autumn. In regard to Y. pseudotuberculosis infection, it is noteworthy that in Finland—in contrast to the situation in Japan—outbreaks were observed throughout the year.

DISCUSSION

The comparison of epidemiologic data on KD and Y. pseudotuberculosis infection published during the past 30 years highlights an epidemiologic overlap of these 2 human pathologies that had not been previously described. The incidence of KD was higher than usual when epidemics or high seasonal rates of Y. pseudotuberculosis infection (indicating an increased risk of contact between the human population and the pathogen) were observed. Given that our work is based on reported cases and that we know nothing about countries where neither KD nor Y. pseudotuberculosis infection is notifiable, the absence of such knowledge does not negate or diminish the importance of the secular and seasonal co-occurrence of both diseases observed in Japan and Finland with high-quality reporting. Parallel increases in winter incidence of both illnesses occur every year in Japan, whereas the poor seasonality of KD in Finland fits with the year-long distribution of Y. pseudotuberculosis infection. Such observations strongly suggest that the disease association is consistent over time and is not merely a result of any independent, secular phenomena. It could be assumed that simultaneous but independent considerations for both conditions could have resulted in increasing reports in the literature. However, in view of sustained public health surveillance for food-borne diseases with improved vigilance and international information exchange, it is unlikely that the interest would have diminished in Japan and not in Finland. None of the epidemiologic publications on Y. pseudotuberculosis infections mentioned any concern for KD, showing that the reports were not related to or prompted by the publicity associated with KD epidemics.

One could argue that this type of seasonal association could be established for other pathogenic microorganisms that spread through populations during the cold periods of the year. Thus, Y. pseudotuberculosis could be merely a risk marker for winter-spring KD, without being involved in the pathogenesis of the disease. However, the temporal association of the 2 illnesses indicates that the link is not only related to annual variations in weather. The disappearance of massive outbreaks in Japan since 1986 or the emergence of KD epidemic in Finland in 1981 cannot be ascribed to any differences between the 2 countries in term of major climate changes. Moreover, a number of viral and bacterial infections occurring in children during winter and spring have been surveyed in Japan at the national level, and none of the changes in incidence matches the variation over time in the epidemiology of KD. For these reasons, a potential confounding effect of cold weather seems unlikely.

As part of current research on this possible infectious origin of KD, our review of the epidemiologic literature...
revealed a hitherto unnoticed element contributing to debate on the potential role of *Y. pseudotuberculosis* infection. In addition to exotoxin production by some strains and the KD-like syndrome observed in some cases of infection, the epidemiology of *Y. pseudotuberculosis* is also consistent with this hypothesis. Recent works have emphasized the possible multiple etiologies of KD, and from this viewpoint, a partial contribution of *Y. pseudotuberculosis* should now be considered.

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