

Original article

Suppressive influence of seasonal influenza epidemic on Kawasaki disease onset

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summary

Kawasaki disease (KD) is an acute systemic vasculitis presenting as an infantile febrile disease. In Japan, the widespread cedar plantation commenced in 1945 has been correlated with the increased incidences of both KD and allergic rhinitis (pollinosis) since the early 1960s. We previously showed that KD was a pollen-induced, delayed-type hypersensitivity that displays biphasic peaks in both summer and winter. KD incidences decrease suddenly around February, particularly after influenza epidemics. Here we investigated the reason for a drastic decrease in KD onsets directly before spring pollen release following rapid increase after autumn pollen release leading to the biphasic pattern. We separately analyzed weekly incidences of KD and influenza in Tokyo (1987–2010) and Kanagawa (1991–2002). Repeated measures for the analysis of variance followed by Bonferroni's multiple comparison tests were performed to compare KD incidence over 3 consecutive weeks, including the weeks when the mean KD prevalence showed the steepest decrease. Next, the week with peak influenza incidence was reset for each year. KD incidence over 3 consecutive weeks, including the new origin week (adjusted week 0), was similarly analyzed. In Tokyo and Kanagawa, KD incidence significantly decreased only after resetting the influenza peak time. These findings suggested that influenza epidemics suppressed KD onset.

Key words—Kawasaki disease; onset; suppression; influenza epidemic; interferon- β

Abbreviations—KD, Kawasaki disease; IDWRs, infectious diseases weekly reports; IFNs, interferons; IVIG, intravenous immunoglobulin; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ANOVA, analysis of variance; DTH, delayed-type hypersensitivity; MS, multiple sclerosis

Introduction

Kawasaki disease (KD) is a systemic vasculitis of unknown cause occurring in infants and children. Since the original report by Kawasaki in 1962, some microorganisms have been implicated in its origin^{1–3}. Further, a relationship between KD and atopy has been examined in a large cohort study⁴ and in a population-based study⁵.

In Japan, widespread cedar planting was commenced after 1945. Environmental pollutions, such as air pollution, had spread during 1950s–1960s due to rapid economic growth and motorization, and both KD and allergic rhinitis (pollinosis) cases were independently reported for the first time during earlier 1960s.

Based on the reports of Kawasaki and Saito on KD and Japanese cedar pollinosis, respectively⁶, at almost similarly earlier 1960s, we have been investigating the association between KD onset and pollen exposure^{7–9}.

The monthly variation in the number of patients with KD (total of approximately 6,000) and of pollen in Kanagawa during 144 months from January 1991–

December 2002 was depicted in figures^{8,9} and supplementary information. After a full-scale and massive seasonal pollen scatter during February–April every year, the number of patients with KD began increasing and reached a plateau from March or April until August; this was followed by a nadir in September or October before the occurrence of sharp peaks from November to February and then drastic decrease during February and March^{8,9}. The sharp peaks in November to February were believed to be due to pollens of premature male flowers that were previously released during October–January before spring. Therefore, infants who developed KD may have undergone repeated and incremental sensitization to pollen exposure every year^{8,9}, and those who were at risk developed KD after an average of 21.4 months from the first pollen exposure⁹. A combination of cross-correlation and trend analyses revealed a positive correlation between the amount of Japanese cedar pollen and KD onset. Based on these findings, we proposed that KD is a pollen-induced, delayed-type hypersensitivity (DTH) disease^{8,9}.

Relevant analysis was necessary to elucidate the reason for a drastic decrease in KD onsets directly before spring pollen release following rapid increase after autumn pollen release leading to the biphasic pattern of incidence, and a study showed that the sudden decrease in KD outbreaks coincided with the peak in the number of patients with influenza around February¹⁰. In this study, monthly comparison was performed, and further analyses were conducted to assess the relationship between weekly variations in KD incidence and variations in the number of patients with influenza in Kanagawa. On the other hand, by focusing on the original data on KD incidence reported in the infectious diseases weekly reports (IDWRs) by Tokyo Metropolis, we comparatively examined the variations in KD and influenza onset and also evaluated the relation between decreased KD incidence and influenza epidemics in Tokyo. Thus, weekly monitoring was possible for the variables to be comparable between Tokyo and Kanagawa¹¹.

The weekly incidence of KD and influenza in Tokyo from 1987 to 2010 and in Kanagawa from 1991 to 2002 were compared by repeated measures of analysis of variance (ANOVA) followed by Bonferroni's multiple comparison tests for three consecutive weeks, including the weeks when the mean values of KD prevalence showed the steepest decrease during influenza epidemics. On statistical examination, the decrease in KD incidence around February was found to be significant in Kanagawa and Tokyo, suggesting that influenza epidemics suppressed KD onset.

Notably, in Tokyo, when the number of patients with seasonal influenza was maximal and when a novel influenza pandemic occurred in the latter half of the year 2009, the trend of increasing annual KD incidence from 1995–2014 transiently decreased.

The suppressive mechanisms during influenza epidemics may have been due to interferons (IFNs); in KD infants who were exposed to repeated pollen exposure, IFNs from influenza may have interfered with the process of DTH that triggers KD onset. Therefore, we hypothesized that IFN- β can be used to actively treat KD, in addition to the established intravenous immunoglobulin (IVIG) therapy^{12, 13}. Clinical trials are underway to determine the possibility of using IFN- β therapy for

acute respiratory distress syndrome (ARDS)^{14, 15}, based on the finding of its effects on hypoxia/ischemia-related inflammation and blood flow resistance¹⁶. IFN- β therapy has also been tested for chronic obstructive pulmonary disease (COPD) and asthma¹⁷ in Europe. The prophylaxis of KD due to influenza vaccination may have to be taken into account.

Methods

(1) Study setting and population:

This study involves Kanagawa Prefecture (henceforth, Kanagawa), with an area of 2,415.47 km² in 2002 and located at the southwest side of Tokyo Metropolis (henceforth, Tokyo) in Japan. In 2007, it ranked second in population (8,893,264 people) after Tokyo. Tokyo, with an area of 2,187.05 km² in 2002, had the highest population (12,692,117 people) in 2007.

(2) Epidemiological data of patients with KD and influenza:

(A) During 1997–2014, the number of patients with KD (abbreviated as KD Pt.Nos. in the figures) in Kanagawa has been second highest after that in Tokyo among all the 47 local governments of Japan. Individual data of 5,917 patients with KD in Kanagawa during 1991–2002, which was surveyed nationwide (Nationwide Surveillance, KD-NS), including the dates of entering hospitals and suffering day periods, were kindly provided by Professors Yosikazu Nakamura and Hiroshi Yanagawa of the Department of Public Health, Jichi Medical University, Tochigi, Japan. We calculated the dates of onset for each patient and summed up the number of patients with KD for each month or week of these 12 years.

Incidentally, in Kanagawa, the number of patients with KD has not been investigated by sentinels of surveillance facilities since the end of 1990s.

(B) The data on the number of patients with KD in Tokyo was obtained from the data of Tokyo IDWRs. The data from 1982 to 13th week of 2000 were kindly provided by Ms. Kahoru Noguchi of the Infectious Disease Surveillance Center, Tokyo Metropolitan Institute of Public Health (Shinjuku-ku, Tokyo). The IDWR data after 14th week of 2000 to 52nd week of 2010 were downloaded from the web¹¹. The number of patients with KD are based on current data of cases reported by sentinels (128,

137, 142, and 150 surveillance facilities in 1987–1990, 1991–1995, 1996–2006, and 2007–2010, respectively). Large amounts of individual data on patients with KD in Tokyo have not been yet supplied by Professors Yosikazu Nakamura and Hiroshi Yanagawa.

(C) Annual number of patients with KD in Kanagawa, Tokyo, and all of Japan from 1970 to 2014 was obtained through web from KD-NS data¹⁸⁾.

(D) Data on weekly reported cases of patients with influenza (Flu Pt. in the figures) by sentinels in ordinance-designated cities of Yokohama city and Kawasaki city, as well as other municipalities, excluding Yokohama and Kawasaki, in Kanagawa were gathered for the first time.

(E) Data on patients with influenza in Yokohama city from 1987 to 2002 were kindly provided by Mr. Yoshiaki Ikemi of Epidemiology and Infectious Diseases Division, Yokohama City Institute of Public Health, Yokohama City. The number of facilities selected as sentinels to influenza was 2,556 to 5,795.

(F) Data on patients with influenza in Kawasaki city from 1991 to 2002 were kindly provided by Mr. Yoshio Muraki of Health and Medical Care Department, Health and Welfare Bureau, Kawasaki City. Thirty-one surveillance facilities were selected as sentinels to patients with influenza.

(G) Data on patients with influenza in other municipalities, excluding Yokohama and Kawasaki, in Kanagawa from 1987 to 2002 were gathered by Mr. Makoto Hayashi of Kanagawa Prefectural Institute of Public Health, but weekly data of 2 to 3 years from 1991 to 2002 was missing; therefore, the data were omitted from the total in this study. Thus, the joint data of both thickly populated Yokohama and Kawasaki were temporarily adopted as the total of the number of patients with influenza in Kanagawa.

(H) The number of patients with influenza in Tokyo was obtained from the data of Tokyo IDWR. The data from 1987 to 13th week of 2000 were kindly provided by Mr. Hiroyuki Taguchi of the Infectious Disease Surveillance Center, Tokyo Metropolitan Institute of Public Health. The IDWR data after 14th week of 2000 to 52th week of 2010 were downloaded from the web. The number of patients with influenza are based on current data of cases reported by sentinels (128, 137, 142, 178,

and 290 surveillance facilities in 1987–1990, 1991–1995, 1996–1998, 1999–2006, and 2007–2010, respectively).

(3) Data on pollens:

Data on the total pollen numbers (count/cm²) of Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtusa*) were surveyed by Dr. Yozo Saito at Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, from 1977 to 1998 and by Dr. Hiroshi Yasueda at National Hospital Organization Sagami-hara National Hospital, Sagami-hara City, Kanagawa, from 1965 to 2003. Tokyo pollens averaging from 12 surveillance points from 1985 to 2015 were downloaded from the web of Tokyo Metropolitan Institute of Public Health¹⁹⁾.

(4) Statistical analysis:

To check the statistical significance of decrease in KD incidence in winter season, the populations in three consecutive weeks with the steepest decrease in mean value were compared by the repeated-measure ANOVA, followed by Bonferroni's multiple comparison test. The significance level was set at 0.05.

Results

The reported KD and influenza incidences in Tokyo from 1987 to 2010 were compared among four separate graphs. The two recent graphs are shown in **Figs. 1a** and **1b**. In 2003, 2005, 2006, and 2008, no KD incidence was distinctly seen for several weeks in February during and/or after the peaks of influenza epidemics.

After the 2008–2009 seasonal influenza epidemic, whose incidence was the largest and long-lasting during the past 24 years (affecting a total of 57,747 people till the 26th week), the swine influenza pandemic, which began in the latter half of 2009 (72, 82, 277, and 1145 people affected at weeks 29, 30, 31, and 53, respectively), reached a peak of 8,073 people at week 44. The incidence of influenza during that period (27–53 weeks) was 84,393 people (maximal incidence), and the annual incidence of influenza was 142,140 people (as shown in **Fig. 1b**). Accordingly, KD incidence up to week 26 diminished by half, with 31 people affected in 2009 compared with the 63 people affected in 2008, and the total KD incidence was 71 people in 2009. In 2010, the

number of people with influenza from weeks 1 to 13 was 1598, 1388, 1908, 1441, 988, 754, 486, 405, 179, 95, 89, 27, and 20, respectively; the epidemic ended without spreading.

Finally, the annual number of incidences was merely 12,614. In particular, there was no seasonal influenza epidemic in Tokyo from 2009 to 2010 owing to the new type of influenza pandemic in the latter half of 2009. Correlating with this trend in influenza incidence, the incidence (101, 110 and 109) of KD cases in 2006–2008 drastically reduced to 71 in 2009 and then increased to 89 in 2010 as shown in **Fig. 1b**; this was probably related to the seasonal influenza epidemic in 2008–2009.

The actual weekly KD incidence by NS-KD and weekly influenza incidence by sentinel reports in Kanagawa were compared; the data on the monthly KD incidence, based on two previous reports^{8,9)}, were converted to weekly data.

To check the statistical significance of the decrease in KD incidence during the influenza epidemic, the style of graphs on the variation in KD incidence was changed (**Figs. 2 and 4**). The weekly variation in KD incidence in Tokyo during 1987–2010 was depicted from one autumn to the following autumn through the 1st week (0 time) of every year, as shown in the center in **Fig. 2a**. Next, adjusting (0 time) the variation in KD incidence for 1 week in every year when the highest influenza incidence occurred, the curves moved in right and left as shown in **Fig. 2b**. The mean number of patients with KD in **Figs. 2a and 2b** were then calculated and plotted in **Figs. 3a and 3b**, respectively.

Similarly, analyses were performed on the weekly variations in the number of patients with KD in Kanagawa during 1991–2002, as shown in **Figs. 4a, 4b, 5a, and 5b**.

The steepest decrease in the mean number of patients with KD for three consecutive weeks was compared before and after time-adjustment with peak influenza incidence both in Tokyo and Kanagawa, as shown in **Table 1**. Across the years, the mean number of patients with KD showed the steepest decrease from weeks 3 to 4 in Tokyo and from weeks 4 to 5 in Kanagawa. After the week with peak influenza incidence was reset to new time origin for each year, the time-adjusted mean number of patients with KD across the years showed the steepest

decrease from the adjusted week –1 to 0 in both Tokyo and Kanagawa. The decrease in the number of patients with KD was significant between adjusted weeks –1 and 1 in both Tokyo and Kanagawa; whereas no significant differences were detected in the incidences among weeks 3, 4, and 5 in Tokyo and among weeks 4, 5, and 6 in Kanagawa. Therefore, significant results were obtained only after adjusting the number of patients with KD at 0 time in the variation curve of the weeks when the highest number of patients with influenza occurred every year (**Table 1**).

Figure 6 shows the actual annual number of patients with KD in Tokyo, Kanagawa, and all of Japan from 1970 to 2014, based on the data from the National Survey group of KD¹⁸⁾ and the observed pollen counts in Tokyo¹⁹⁾ and Kanagawa (Methods(3)). The amount of pollen release and number of patients with KD began increasing from 1979 in Japan; with global warming, the number of patients with KD increased until 2014. As scales of all the Japan incidence were used as 10 times those of Tokyo, it was clearly seen about 10% of the nationwide incidence in Tokyo, for many years. There was a remarkable decline in the number of patients with KD in 2009, at a glance, because of the record-high seasonal influenza epidemic in Tokyo and the new influenza pandemic all over Japan in 2008–2009. This implied that the influenza epidemic suppressed KD onset in 2009 and partly delayed it in 2010.

Discussion

Pollens from anemophilous flowers are ubiquitous. Based on our epidemiologic analyses of the annual pattern in KD onset, we presumed that the causative substance involved in and responsible for KD onset may be pollens, particularly cedar pollen in Japan⁸⁾, and that one of the suppressive factors to KD onset may be influenza epidemics. By the way, the prevalent time of Respiratory syncytial virus (RSV) infection is from October to December (data not shown¹¹⁾), and so RSV is supposed not to be relevant to the phenomenon around February. Based on our previous study^{7–9)}, we propose that pollen exposure influences the mechanism of KD onset, which is described in **Fig. 7**²⁰⁾. To validate this hypothesis, the creation of new animal models of KD using Japanese cedar pollen and its constituents, such as

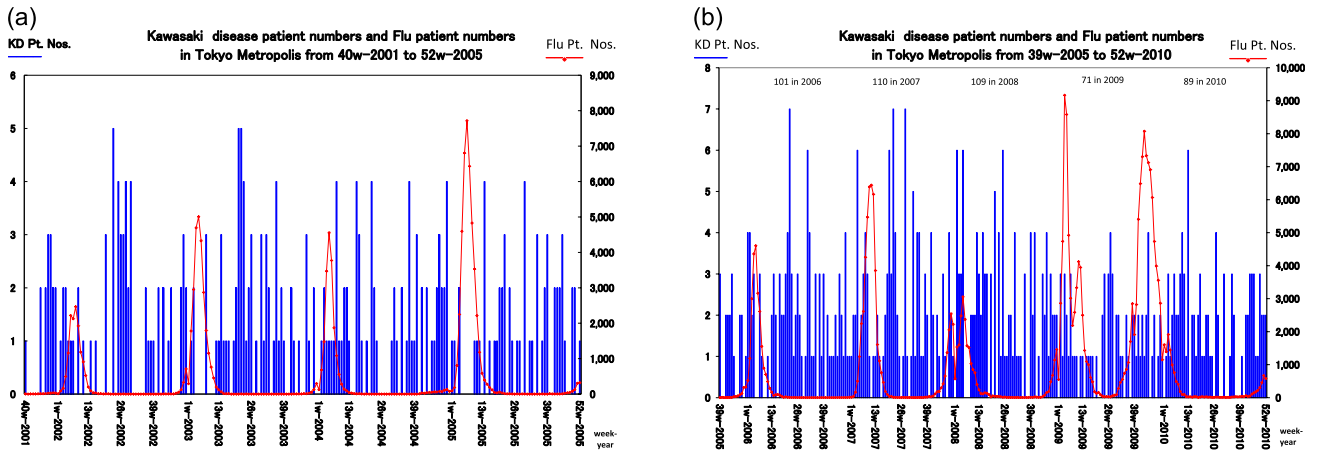


Fig. 1 The reported number of Kawasaki disease (KD) and influenza patients in Tokyo infectious diseases weekly reports (IDWRs) gathered from 2001 to 2010
 a. Variation from week 40 of 2001 to week 52 of 2005; b. Variation from week 39 of 2005 to week 52 of 2010.

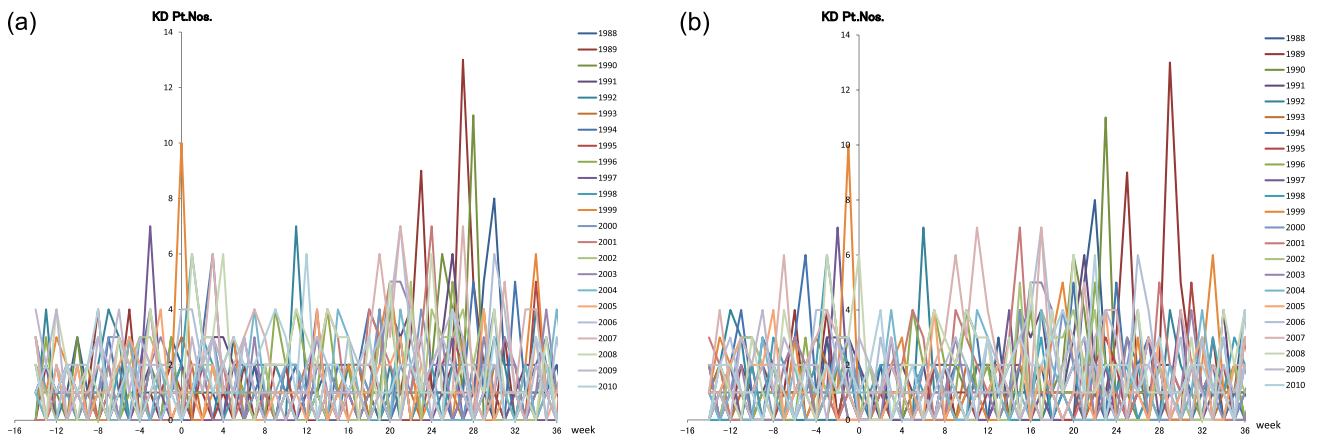


Fig. 2 Weekly variations in the number of patients with Kawasaki disease (KD) in Tokyo from 1987 to 2010
 a. Annual number of KD patients is shown from one autumn to the following autumn through the 1st week (0 time) of every year, as shown in the center.
 b. Variation in the number of KD patients adjusted to 0 time on the week when the most number of patients with influenza occurred every year; curves moving back and forth.

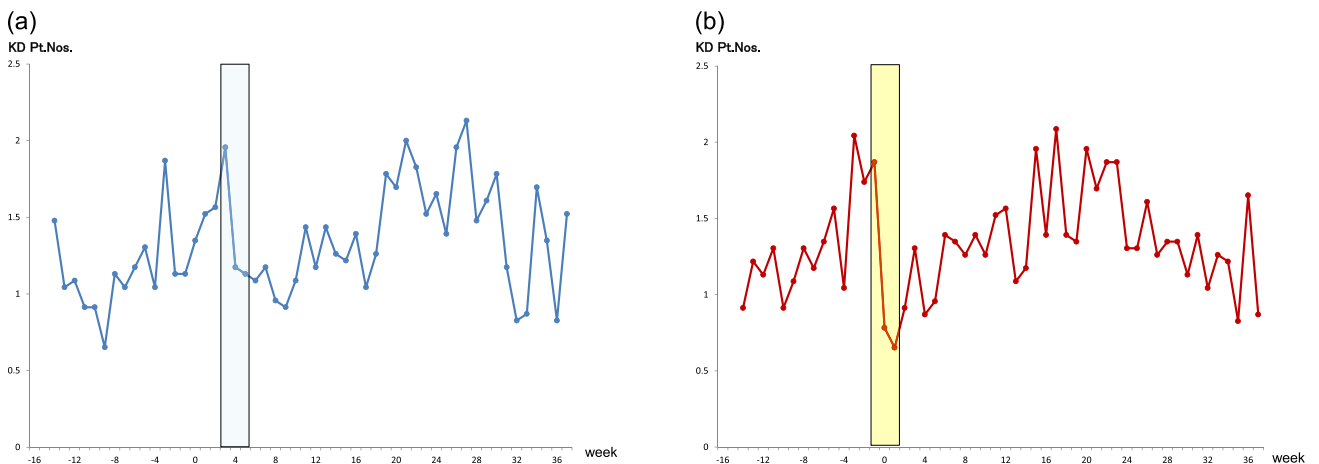


Fig. 3 Weekly variations in the mean number of patients with Kawasaki disease (KD) in Tokyo from 1987 to 2010
 a. Annual mean number of KD patients is shown from one autumn to the following autumn through the 1st week (0 time) of every year, as shown in the center.
 b. Variation in mean number of KD patients adjusted to 0 time on the week when the highest number of patients with influenza occurred every year; curves moving back and forth.

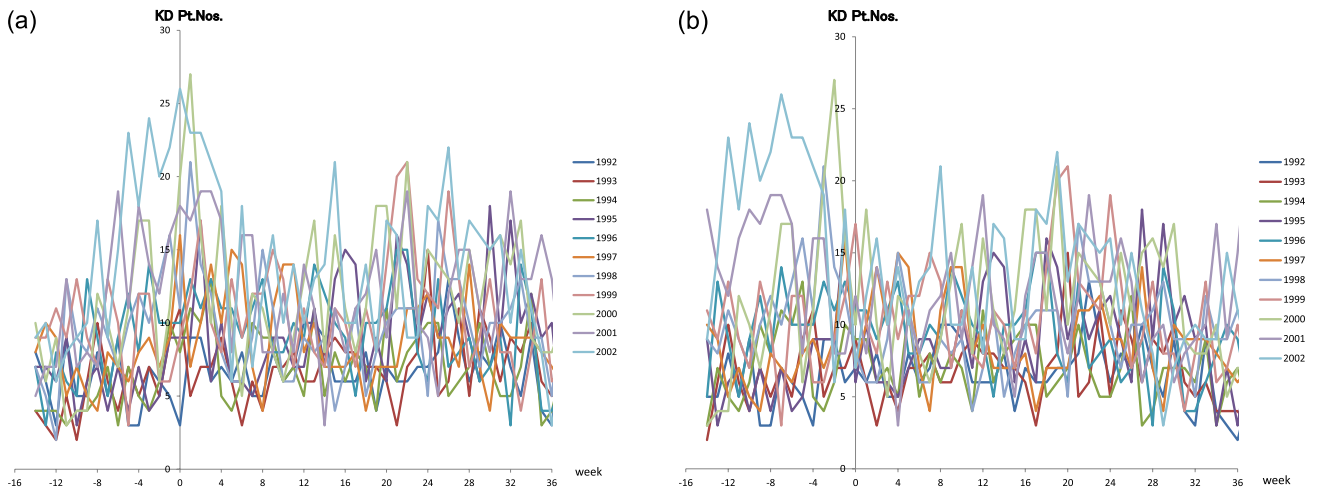


Fig. 4 Weekly variations in the number of Kawasaki disease (KD) patients in Kanagawa from 1991 to 2002

- a. Procedure similar to that described in the legend to Figure 2a was conducted.
- b. Procedure similar to that described in the legend to Figure 2b was conducted.

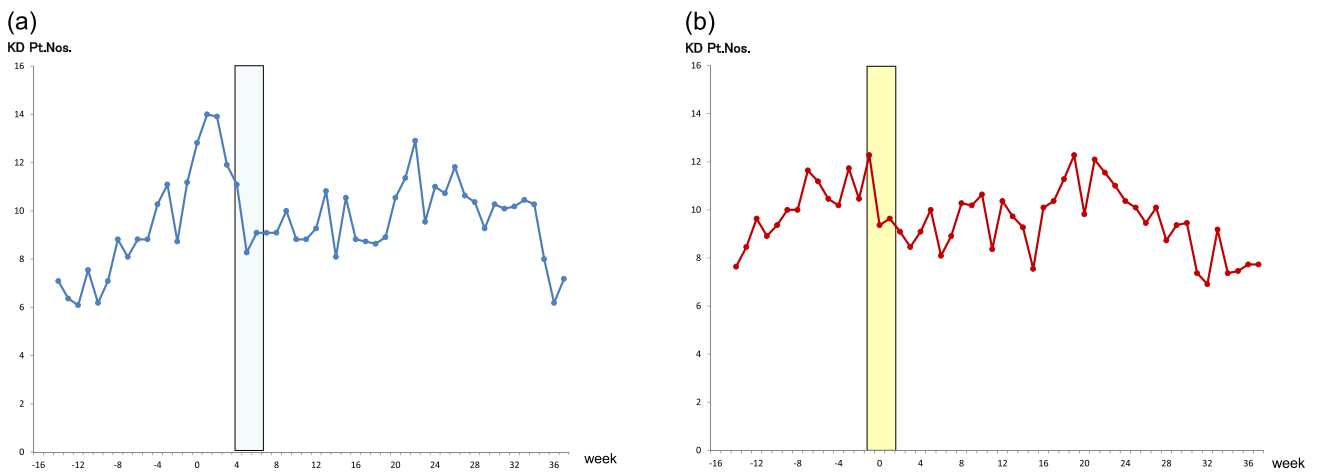


Fig. 5 Weekly variations in the mean number of Kawasaki disease (KD) patients in Kanagawa from 1991 to 2002

- a. Procedure similar to that described in the legend to Figure 3a was conducted.
- b. Procedure similar to that described in the legend to Figure 3b was conducted.

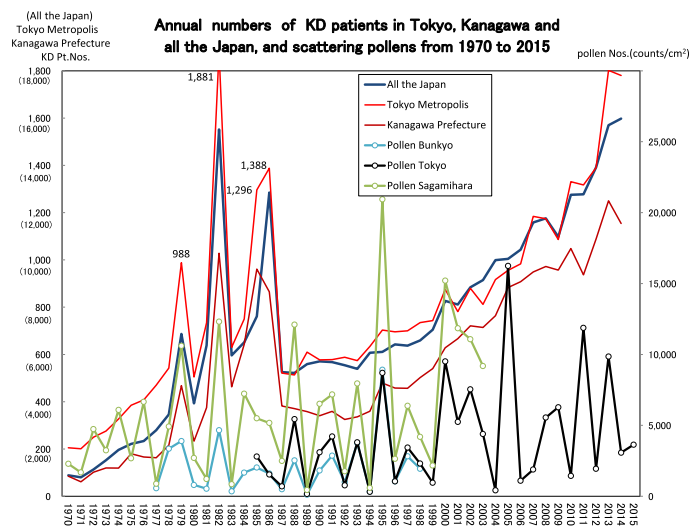


Fig. 6 The annual number of Kawasaki disease (KD) patients in Tokyo, Kanagawa, and all of Japan and the pattern of pollen scattering from 1970 to 2015

The actual annual number of KD patients in the Tokyo, Kanagawa, and all of Japan from 1970 to 2014 and the observed pollen counts in Tokyo and Kanagawa from 1970 to 2015 are shown.

Table 1. Comparison of Kawasaki disease (KD) incidence in Tokyo and Kanagawa among three consecutive weeks from 1987 to 2010 and from 1991 to 2002, respectively

Region	week	N	mean	SD	SEM	Multiple comparison (Bonferroni)			
						weeks compared		p-value	significance
Tokyo	week 3	23	1.957	1.745	0.364	week 3	week 4	0.2120	ns
	week 4	23	1.174	1.370	0.286	week 3	week 5	0.1780	ns
	week 5	23	1.130	1.058	0.211	week 4	week 5	1.0000	ns
	adjusted week -1	23	1.870	2.052	0.428	adjusted week -1	adjusted week 0	0.1160	ns
	adjusted week 0	23	0.783	1.413	0.295	adjusted week -1	adjusted week 1	0.0430	*
	adjusted week 1	23	0.652	0.832	0.173	adjusted week 0	adjusted week 1	1.0000	ns
Kanagawa	week 4	11	11.091	4.742	1.430	week 4	week 5	0.3690	ns
	week 5	11	8.273	3.495	1.054	week 4	week 6	0.5240	ns
	week 6	11	9.091	4.847	1.461	week 5	week 6	1.0000	ns
	adjusted week -1	11	12.273	4.174	1.258	adjusted week -1	adjusted week 0	0.1250	ns
	adjusted week 0	11	9.364	3.139	0.947	adjusted week -1	adjusted week 1	0.0170	*
	adjusted week 1	11	9.636	3.472	1.047	adjusted week 0	adjusted week 1	0.8410	ns

N: sample size, SD: standard deviation, SEM: standard error of the mean, ns: non-significant, *significant with $p < 0.05$.

Cry j 1, Cry j 2, or other proteins^{21, 22)}, would be ideal. In addition, it is important for advanced clinicians to test blastoid transformation or to perform lymphocyte stimulation tests in patients with KD in the acute phase to search for lymphocytes sensitized by pollen antigens^{23, 24)}. An immunologically interesting problem is whether the components of Japanese cedar pollen induce concurrent or separate immediate type-1 allergic reactions, such as allergic rhinitis or conjunctivitis, after KD onset, which is presumed to develop as DTH or type-4 allergy (cellular immunology)^{25, 26)}.

We understand that the phenomenon of the coincidence of a characteristically sharp transient valley of the number of patients with KD and peak of the number of patients with influenza around February means ‘the process of sensitization by first pollen exposure → re-sensitization with subsequent pollen exposures → DTH maturation → KD onset’, which is suppressed or delayed by Type I IFNs, particularly IFN-β probably induced during innate immunity-mediated process in nursing infants by subclinical influenza infection or environment in influenza epidemic²⁷⁾.

Focusing on IFN-β, which has been prescribed and designated as safe for multiple sclerosis (MS) and hepatitis, we noticed that IFN-β action in MS was partly due to its anti-inflammatory effects on cerebral vessels²⁸⁾. Further, Veldhuis¹⁶⁾ and Jalkanen²⁹⁾ independently reported that hypoxia/ischemia-related inflammation, blood flow resistance, and ischemia reperfusion injury were symp-

tomatically treated using IFN-β. Recently, in Europe, clinical trials on the use of IFN-β for ARDS, COPD, and asthma have been started^{15, 17)}. These studies suggested a high probability that Type I IFNs interfere with the process of KD onset and prevent coronary artery abnormalities in patients with KD. Therefore, we hypothesized that IFN-β may be used to actively treat KD, in addition to the established IVIG therapy. This hypothesis needs to be tested first in translational studies to determine its applicability to animal models and clinical trials on IVIG-resistant KD.

In many countries, influenza vaccination is provided every year for prophylaxis and during influenza epidemics^{30, 31)}. Our results indirectly suggested that influenza vaccination may suppress KD onset in winter and delay it in spring. For practical clinical application, influenza vaccine may be administered to block the progression of systemic vasculitis in patients at risk for KD due to repeated pollen sensitization.

From another viewpoint, it is known that at the time of KD onset, inflammation at the Bacille de Calmette et Guérin (BCG) vaccination site (i.e., BCG reactivation, such as skin redness, swelling reaction similar to those observed with tuberculin, ulceration, and lesion) is observed in patients who have not undergone tuberculin skin tests that manifest DTH to BCG constituents⁹⁾. Thus, the suppressive effects of influenza vaccine on systemic augmentation or maturation of DTH due to pollen exposure in patients at risk for KD onset may also interfere

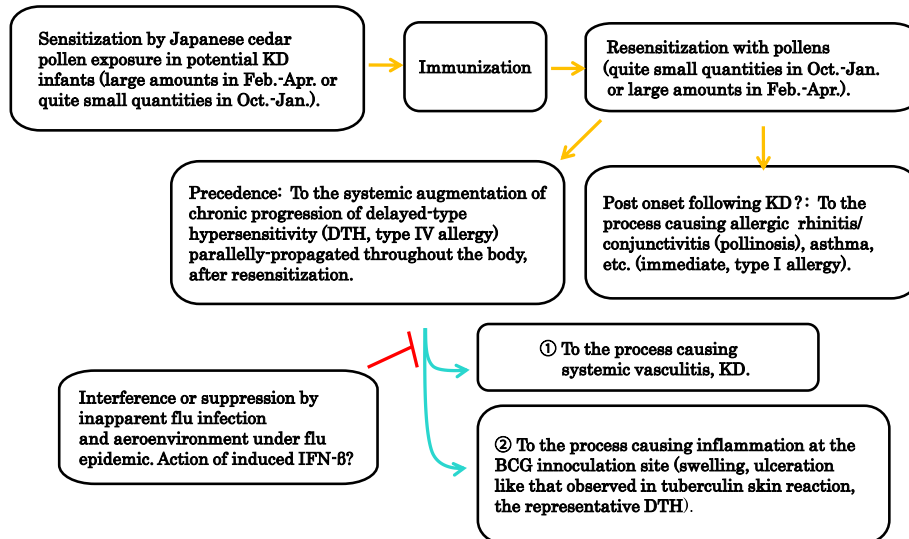


Fig. 7 The putative process leading to onset of Kawasaki disease (KD), a systemic vasculitis that is one of the pollen-induced diseases (PID)

Supplementary Information

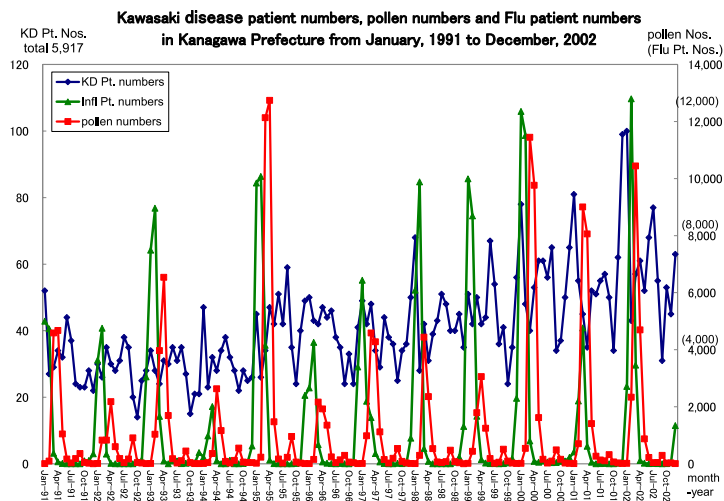


Fig. 8 The number of Kawasaki disease (KD) and influenza patients and pollens in Kanagawa from January 1991 to December 2002. Monthly variations in the number of patients with KD and influenza, and pollens in Kanagawa are shown.

with DTH to other microbial vaccines, including BCG³²⁾.

It is necessary for physicians to examine these possibilities and to determine the adequate intervals among various vaccinations in animal tests and clinical trials.

Conclusions

(A) Several case reports have presented the relation between microbial infection and KD onset at the similar time, and further KD onset after vaccination with some microbials. However, our present report may be the first one showing the suppressive effect of influenza epidemic on KD onset.

(B) This finding would promote researchers to accel-

erate studies on the process of immunological augmentation slowly leading to the onset of systemic vasculitis, KD which could be blocked by interferon- β possibly generated in nursing infants in response to subclinical influenza infection or environment in influenza epidemic.

(C) Our epidemiological results can be substantiated using animal models of KD, i.e., mice immunized with pollens, and by further experiments on influenza virus infection or vaccination.

(D) Clinical trial of interferon- β therapy for KD and of influenza virus vaccination to prevent KD will be considered.

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Author Contributions

Akira Awaya designed this study, performed the work, and wrote this manuscript.

Conflicts of Interest

The author declares no conflict of interest.

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