

# Evaluation of the Temporal Association between Kawasaki Disease and Viral Infections in South Korea

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**Background and Objectives:** This study is aimed at elucidating potential temporal associations between the occurrence of Kawasaki disease (KD) and various viral infections.

**Subjects and Methods:** We obtained monthly patterns of KD from the seventh nationwide survey and viral detection data from the Korea Centers for Disease Control and Prevention from 2009 to 2011 and evaluated temporal correlations between them for each month. The respiratory viruses detected using a multiplex real-time-polymerase chain reaction kit were influenza virus (A/H1N1, A/H3N2, A/H5N1, and B), adenovirus, parainfluenza virus (type 1, 2, 3), respiratory syncytial virus (type A, B), human rhinovirus, human coronavirus (OC43/229E, NL63), human bocavirus, and enterovirus.

**Results:** We obtained data from a total of 13031 patients who were treated for acute KD from 87 hospitals with pediatric residence programs. During this survey, KD showed highest overall incidence in summer and winter seasons and lowest incidence in February and October. We received viral detection data for a total of 14267 patients. Viral detection was highest during winter and spring seasons. The most commonly detected virus was human rhinovirus (32.6%), followed by influenza virus (26.8%). The monthly incidence of KD showed significant correlation with the monthly overall viral detection ( $p=0.022$ ,  $r=0.382$ ). In particular, human bocavirus and enterovirus have significant correlations with monthly patterns of KD occurrence ( $p=0.032$  and  $p=0.007$ , respectively) and influenza virus correlated with KD occurrence with borderline significance ( $p=0.063$ ).

**Conclusion:** The temporal association between monthly occurrence of KD and viral detection suggests the etiologic importance of precedent infection in the development of KD. (*Korean Circ J* 2014;44(4):250-254)

**KEY WORDS:** Kawasaki disease; Infection; Association.

## Introduction

Kawasaki disease (KD) is an acute systemic self-limited vascular

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• The authors have no financial conflicts of interest.

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inflammation that mostly affects children less than 5 years of age. It is the most common cause of acquired heart disease in children from developed countries and has devastating complications on the coronary artery such as coronary aneurysm and myocardial infarct.<sup>1-3</sup> Interestingly, KD occurrence shows a specific geographic pattern, with the highest incidence in Northeast Asia, including Japan, Korea, Taiwan and even in Japanese people in Hawaii.<sup>4</sup> KD predominantly occurs in the winter season and shows relatively high incidence in the summer season, but the lowest incidence in October in Japan and South Korea.<sup>5(6)</sup> Both of these epidemiologic features suggested that some kind of infection is one of the causes of KD.<sup>7</sup> While several researchers have reported diverse organisms as the causative agents of KD,<sup>8-11</sup> a definitive cause has not been identified.

To reveal potential temporal associations between KD and various

viral infections, we compared the monthly patterns of KD from the nationwide survey in South Korea with monthly patterns of viral infection from the data obtained from the Laboratory of Respiratory Viruses at the Korea Centers for Disease Control and Prevention between January 2009 and December 2011.

### Subjects and Methods

Under the purview of the Korean Kawasaki Disease Study Group, a nationwide survey was carried out to identify the incidence of KD in South Korea concerning acute KD patients who were hospitalized between January 2009 and December 2011. To determine the incidence of KD, questionnaires were sent to 100 hospitals which have pediatric residency programs. Of the 100 hospitals surveyed, 87 responded. The incidence of KD per month was tallied from January 2009 to December 2011.

Over the same time period, respiratory viral data of patients with acute respiratory symptoms was obtained from the Korea Centers for Disease Control and Prevention. The Laboratory of Respiratory Viruses at the Korea Centers for Disease Control and Prevention has operated the Korea Influenza and Respiratory Viruses Surveillance System since 2009. Respiratory viral detection data are reported weekly. Respiratory specimens from patients with acute respiratory symptoms from 91 primary and secondary medical institutions from around the country were analyzed using a multiplex real-time-polymerase chain reaction (PCR) kit.<sup>12)</sup> Viral detection data from the reports collected between January 2009 and December 2011 were analyzed by month. The viruses detected were as follows: influenza virus (A/H1N1, A/H3N2, A/H5N1, and B), adenovirus, parainfluenza virus (type 1, 2, and 3), respiratory syncytial virus (RSV type A, B), human rhinovirus, human coronavirus (OC43/229E, NL63), human bocavirus, and enterovirus.

This study was approved by the Institutional Review Board of Seoul National University Hospital, and informed consent was waived because of the retrospective nature of this study.

### Statistical analysis

All statistical analyses were performed by using the SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA). Bar graphs and scatter plot were used to examine the temporal pattern and correlation in KD incidence and viral infection. Pearson correlation coefficients were used to investigate the temporal relationship between the number of KD incidence and viral detection rates. One-way analysis of variance (ANOVA) or two-sample t-test was used to examine the significant differences in mean KD incidence or viral infection between seasons or months. Seasons were considered by four groups based on the month: spring (March, April, May), sum-

mer (June, July, August), autumn (September, October, November), and winter (December, January, February). Graphs were produced using Microsoft Excel and STATA 11.0 software (STATA, College Station, TX, USA). A value of  $p < 0.05$  were considered statistically significant.

### Results

#### Monthly pattern of Kawasaki disease

Monthly pattern of KD incidence for the 3 year study period is shown in Fig. 1. KD showed the highest incidence in the summer (most commonly in July) and winter (most commonly in December) seasons.<sup>13)</sup> While ANOVA test for overall differences in KD incidence by seasons was not significant ( $p = 0.12$ ), the differences between summer and autumn were significant ( $p = 0.006$ ). Interestingly, occurrence of KD showed another peak in March due to an abnormally high incidence in March 2010 compared with the incidence in March 2009 and March 2011. The incidence of KD was the lowest in February and October with the same pattern repeating each year. ANOVA F-test for overall differences in mean KD incidence by months was marginally significant ( $F = 2.12, p = 0.06$ )

#### Monthly distribution of viral detection

A total of 14267 respiratory virus cases were detected during the survey period (2435 in 2009; 6614 in 2010; and 5218 in 2011). Monthly distribution of respiratory viral detection over 3 years is shown in Fig. 2. Because influenza virus was epidemic in the spring of 2010 (March: 275 cases, April: 990 cases, May: 193 cases), December 2010 (936 cases), and January 2011 (752 cases), the viral

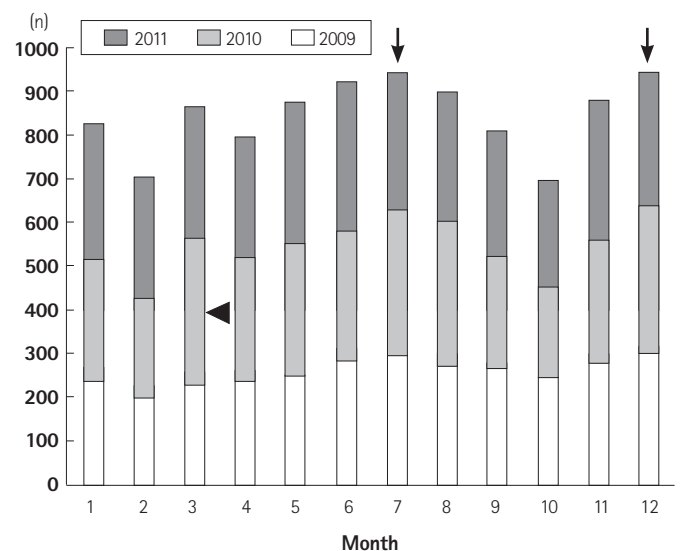
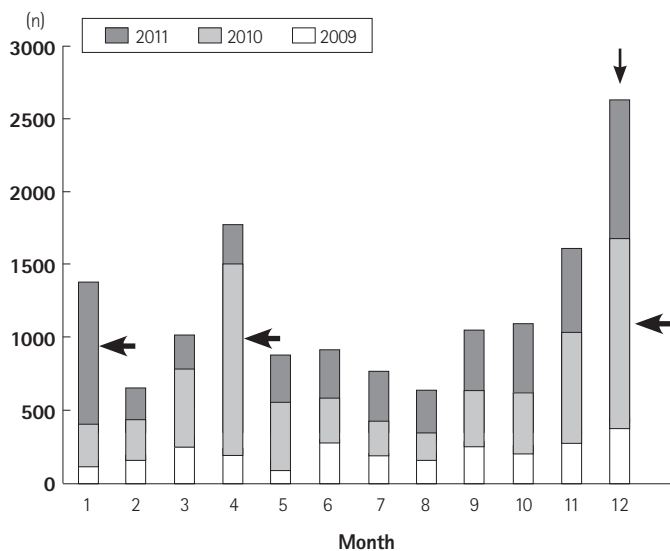


Fig. 1. Monthly patterns of Kawasaki disease occurrence. Kawasaki disease occurred most frequently in summer (arrow, especially July) and winter (arrow, especially December) seasons except for March 2010 (arrowhead). Kawasaki disease occurred least often in February and October.

detection rate was the highest in December, April, and January (Fig. 2). In most other months, fewer than 30 cases of influenza virus were detected (notably, no case was detected in October 2009, July and August 2010, and August 2011). The most common virus detected was human rhinovirus (4648 cases, 32.6%), followed by influenza virus (3827 cases, 26.8%). The parainfluenza virus was detected



**Fig. 2.** Monthly patterns of viral detection. Viral detection was the highest during the winter season (especially December, thin arrow) and relatively high in the spring season. Because influenza virus was epidemic in the spring of 2010, December 2010, and January 2011 (thick arrows), viral detection rates were the highest in December, April, and January. In contrast, viral detection rate was the lowest in February and August throughout the survey period.

the least during this period (382 cases, 2.7%).

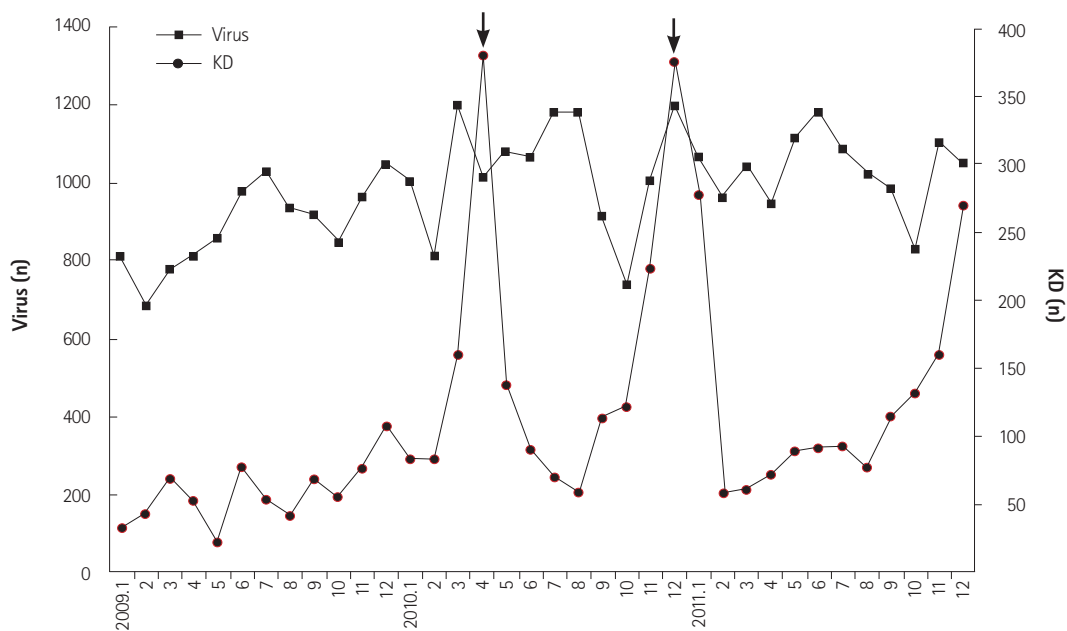
**Correlation between monthly Kawasaki disease incidence and viral detection**

The correlation between monthly KD occurrence and monthly viral detection is presented in Table 1. These patterns are graphed by month in Fig. 3. The monthly incidence of KD showed strong positive correlation with the monthly overall viral detection on the scatter plot shown in Fig. 4 ( $r=0.382$ ,  $p=0.022$ ). In particular, incidence of human bocavirus and enterovirus correlated significantly with monthly patterns of KD occurrence ( $p=0.032$  and  $p=0.007$ , respectively) (Fig. 5). Monthly patterns of influenza virus and KD occurrence

**Table 1.** Temporal relationship between monthly Kawasaki disease occurrence and viral detection rates in 2009–2011 in Korea

Virus	Correlation coefficient (r)	p*
Adeno virus	0.173	0.312
Parainfluenza virus	0.273	0.107
RS virus	0.108	0.530
Influenza virus	0.313	0.063
Corona virus	0.115	0.505
Rhino virus	0.505	0.734
Boca virus	0.359	0.032
Entero virus	0.483	0.007
Total virus	0.382	0.022

\*p are obtained from the Z-test for Pearson's correlation coefficient. RS: respiratory syncytial



**Fig. 3.** Correlation between monthly patterns of occurrence of Kawasaki disease (KD) and viral detection. There are 2 definite peaks of viral detection in April and December 2010 due to influenza virus epidemics (arrows).

correlated with borderline significance ( $p=0.063$ ).

## Discussion

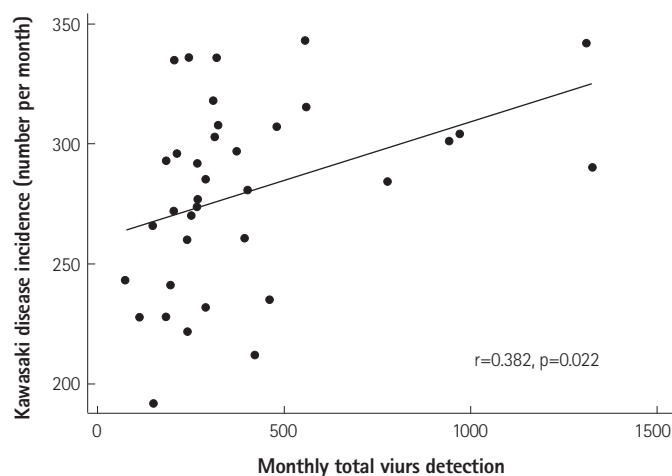
As an acquired heart disease in Children, KD has a special importance not only because of the high incidence in children but also the devastating sequelae in the coronary artery such as coronary aneurysm, myocardial infarction, and even sudden death.<sup>2)3)</sup> According to our recent nationwide retrospective survey between 2009 and 2011, a total of 13031 patients were diagnosed with acute KD and the average annual incidence of KD was 127.7 per 100000 in children less than 5 years of age.<sup>13)</sup> Furthermore, the overall incidence of KD is increasing every year in South Korea.<sup>6)13)</sup>

Up to now, the definite etiology of KD is unknown, however, various epidemiological data have suggested that certain infectious

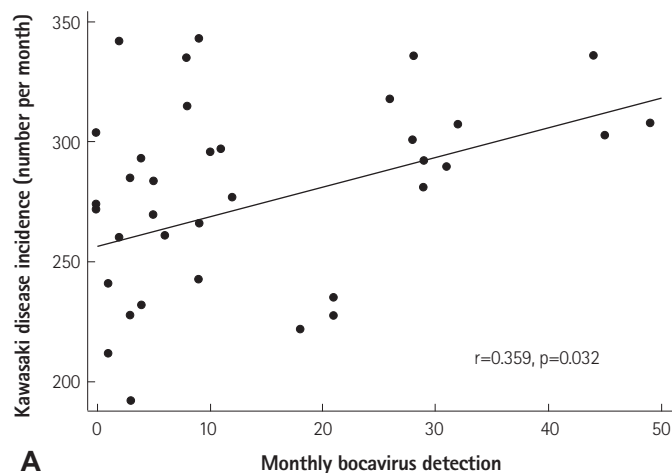
agents might be factors that provoke the onset of KD in those with a genetic predisposition to its pathogenesis.<sup>3)5)14)</sup> The temporal correlation between monthly patterns of KD occurrence and viral detection from the national data acquired for this study also favors an association of infectious disease with the pathogenesis of KD. In particular, monthly detections of human bocavirus and enterovirus showed significant indirect correlations with KD occurrence. Several studies have shown that human bocavirus may play a pathogenic role in the development of KD using direct specimen tests from KD patients.<sup>10)15)</sup> The association with enterovirus such as coxsackie virus and KD occurrence also has been suggested from several case series.<sup>11)16)</sup>

For evaluating the direct association between the occurrence of KD and viral infection, several studies have tried to detect certain viruses in patients with acute KD. Using direct fluorescent antibody assays, Jordan-Villegas et al.<sup>17)</sup> reported that 8.8% of 251 KD patients studied were positive for more than one of 7 different viral respiratory infections (RSV; parainfluenza virus types 1, 2, and 3; influenza virus A and B; and adenovirus). Using multiplex real-time-polymerase chain reaction (PCR), Cho et al.<sup>18)</sup> also revealed that 22% of acute KD patients tested positive for more than one of 11 respiratory viruses {RSV; adenovirus; rhinovirus; parainfluenza viruses 1 and 3; influenza viruses A and B; human metapneumo virus; human bocavirus; and human coronavirus (OC43/229E, NL63)}.<sup>18)</sup> However, these rates of viral infection showed no differences between acute KD patients and febrile patients without KD in a small case-control study (32.7% in 55 acute KD patients versus 30.8% in 78 febrile patients without KD) using a multiplex real-time-PCR assay.<sup>19)</sup> These reports support the hypothesis that various infectious agents are involved in the onset of KD, but do not cause KD directly.<sup>2)14)</sup>

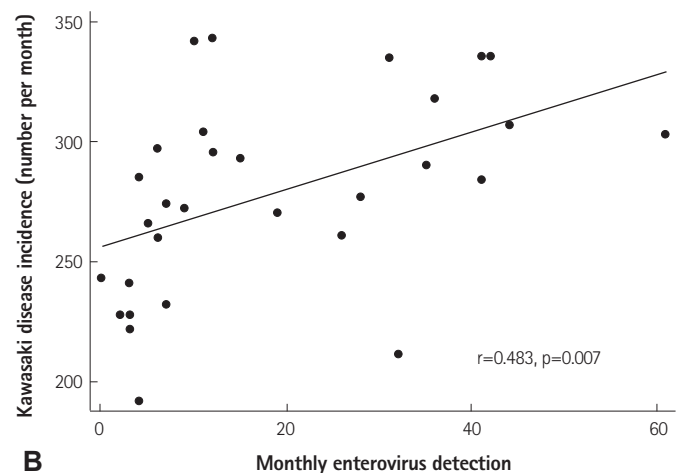
According to the data collected for this study, incidents of KD in South Korea are highest in the summer and winter seasons (most



**Fig. 4.** Scatter plot of monthly Kawasaki disease incidence and viral detection. The scatterplot between monthly occurrence of Kawasaki disease and total viral detection rates show a strong positive correlation ( $r=0.382$ ,  $p=0.022$ ).



**A**



**B**

**Fig. 5.** Monthly Kawasaki disease incidence and the detection of bocavirus (A) and enterovirus (B). Human bocavirus and enterovirus show significant correlation with monthly patterns of Kawasaki disease occurrence on scatter plot diagram ( $p=0.032$  and  $p=0.007$ , respectively).

prominent in July and December) and was the lowest in February and October.<sup>13)</sup> This pattern agrees with a previous study in South Korea and a nationwide survey in Japan.<sup>6)20)</sup> However, viruses that were prominently detected in the winter season were detected at relatively low rates in the summer season throughout the survey period. At this time, there is no explanation for the discrepancy between the high incidence of KD and the low viral detection during the summer season. This may suggest the existence of causative agents for KD other than well-known detectable organisms. A subsequent study is underway that will attempt to find a causative airborne pathogen for KD by filtering the air over Japan at various altitudes during a period when the agent is suspected to be present.<sup>21)22)</sup>

Several factors limit the efficacy of this study. First, the design of this study does not allow for the accurate assessment of individual patient-level association between viral infection and occurrence of KD. Future studies should include meticulously designed large-scale prospective studies using specimens from KD patients. Additionally, the Laboratory of Respiratory Viruses at the Korea Centers for Disease Control contributed data from only 91 primary and secondary medical institutions and may not be representative of all viral infection cases in South Korea.

In conclusion, the temporal association between the monthly occurrence of KD and the detection of viruses suggests the etiologic importance of precedent infection in the development of KD. However, meticulously designed large-scale prospective studies using specimens from acute KD patients are necessary to elucidate an accurate causality between particular infectious agents and the occurrence of KD.

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