“Spike” in acute asthma exacerbations during enterovirus D68 epidemic in Japan: A nation-wide survey

Seigo Korematsua, Kengo Nagashimab, Yasunori Sato b, Mizuho Nagao c, Shunji Hasegawad, Haruna Nakamura c, Shiho Sugiiroc, Katsushi Miuraf, Kenji Okadag, Takao Fujisawac, a, on behalf of the Japanese Society of Pediatric Allergy and Clinical Immunology

Introduction

Implementation of asthma guidelines endorsing anti-inflammatory treatment has improved control of asthma and drastically reduced asthma-related deaths around the world. However, acute exacerbation of asthma is still one of the leading causes of hospitalization of young children, and the majority of those exacerbations are associated with viral respiratory infections. Among the respiratory viruses that cause acute asthma exacerbation, the Picornaviridae, which include human rhinovirus and enterovirus, are known to be major culprits. They usually cause common colds or upper respiratory infections, but they sometimes infect and replicate in the lower respiratory tract of susceptible individuals. Then, in some of those individuals with asthma, the host inflammatory response aberrantly leads to acute exacerbation.1 Johnston et al.

Acknowledgment

The spike in pediatric asthma hospitalizations in Japan in September 2015 was found to be associated with the EV-D68 detections for asthma exacerbation. Respiratory pathogens can cause “epidemics” of asthma exacerbation. Coordinated surveillance of infectious diseases and asthma may be beneficial for prevention and better control of both illnesses.

* Corresponding author. Institute for Clinical Research, Mie National Hospital, 357 Osato-kubota, Tsu, Mie 514-0125, Japan. E-mail address: fujisawa@mie-m.hosp.go.jp (T. Fujisawa).

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List of abbreviations used:

EV-D68, enterovirus D68; AF, acute flaccid paralysis; SPCRI, the Japanese Society of Pediatric Allergy and Clinical Immunology; MV, mechanical ventilation; ICU, intensive care unit; IDSC, the Infectious Disease Surveillance Center

Background: In September 2015, Japan experienced an unusual increase in acute asthma hospitalizations of children that coincided with an enterovirus D68 (EV-D68) epidemic. The objective of this study is to investigate whether EV-D68 had a causal relationship with the spike in asthma hospitalizations.

Methods: A nation-wide retrospective survey of asthma hospitalizations of children was performed for the period from January 2010 through October 2015. The Japanese Society of Pediatric Allergy and Clinical Immunology asked its affiliated hospitals to report monthly numbers of hospitalizations, ICU admissions and mechanical ventilations due to acute asthma exacerbation. The data were retrieved from medical databases using predefined search criteria: diagnosis of asthma or asthmatic bronchitis, admission, and age <20 years. Monthly numbers of EV-D68 detection were also obtained from the Infectious Disease Surveillance Center of Japan. A Granger causality test was used to analyze the association of EV-D68 detections for asthma exacerbation.

Results: A total of 157 hospitals reported 87,189 asthma hospitalizations, including 477 ICU admissions and 1193 mechanical ventilations, during the survey period of 5 years and 10 months. The numbers of these events increased drastically in September 2015. The Granger causality test verified the association between EV-D68 and asthma hospitalizations/mechanical ventilations. The most-affected age group was 3–6 years old.

Conclusions: The spike in pediatric asthma hospitalizations in Japan in September 2015 was found to be associated with the EV-D68 epidemic. Respiratory pathogens can cause “epidemics” of asthma exacerbation. Coordinated surveillance of infectious diseases and asthma may be beneficial for prevention and better control of both illnesses.

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reported that approximately 60% of acute asthma exacerbations were attributable to a Picornaviridae epidemic.  

In Japan in September 2015, an unusual increase in acute asthma hospitalizations occurred in many pediatric hospitals. During the same period, four consecutive severe asthma patients who needed intensive treatment including mechanical ventilation were reported at one center in Tokyo, and enterovirus D68 (EV-D68) was detected in all four patients. In addition, sporadic cases of polio-like acute flaccid paralysis (AFP) were also reported to be associated with EV-D68. In response to these serious events, Japan’s Ministry of Health, Welfare and Labour initiated emergency measures to actively survey AFP in relation to EV-D68. In regard to asthma exacerbation, however, due to a lack of baseline data on the prevalence of asthma exacerbation, the government was not prompted to actively investigate the relationship between the September “spike” in asthma hospitalizations and the 2015 EV-D68 endemic. 

EV-D68, a member of the Picornaviridae family, had been an “inconspicuous” rare pathogen. However, several 2014 events related to EV-D68, including an outbreak of severe respiratory illness in Missouri and Illinois in the United States, an epidemic in Denmark and a cluster of AFP in Colorado, USA, resulted in issuance of a global public health alert. In this context, it seemed very likely that EV-D68 was associated with the acute asthma exacerbation “spike” in September of 2015 in Japan. To clarify the impact of EV-D68 on asthma, we performed a nation-wide survey of asthma hospitalizations in Japan. Although the survey was done in a retrospective manner, this is the first nation-wide epidemiological study focused on acute asthma exacerbations in children. We found a significant increase in acute asthma hospitalizations of children in September of 2015 in Japan that coincided with the EV-D68 epidemic.

Methods

In response to information of an unusual increase in asthma hospitalizations in September 2015, the Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) planned and then initiated, on November 11, 2015, a nation-wide survey of asthma hospitalizations of children in Japan. The JSPACI has over 4000 members in Japan, a majority of whom are pediatricians who are actively involved in asthma treatment. Through its web site and email, the JSPACI asked its members to retrospectively survey pediatric asthma hospitalizations from January 2010 to October 2015. The survey covered patients under 20 years of age who were hospitalized due to acute asthma exacerbation during the period. The data were retrieved from the medical databases of each hospital, using two predefined criteria: 1) diagnosis of asthma or asthmatic bronchitis, and 2) hospital admission. Patients who need admission and/or mechanical ventilation, including nasal high flow and nasal continuous positive airway pressure, were also searched. Patients were stratified for gender and age group (0–2, 3–6, 7–12 and 13–19 years old) in each month throughout the survey period. A FP cases in 2015 at each hospital, regardless of asthma hospitalization, were also surveyed, and the presence or absence of wheezing in the AFP cases was elucidated. 

Separately, national surveillance data on EV-D68 detection were obtained from the Infectious Disease Surveillance Center (IDSC) at National Institute of Infectious Diseases, Japan (http://www.nih.go.jp/niiid/en/, last accessed on 1st November 2016). No personal information was collected. Moreover, this study did not fall within the scope of the 2014 Ethical Guidelines for Medical and Health Research Involving Human Subjects by Ministry of Health, Welfare and Labour and Ministry of Science and Education, Japan, because it utilized information that had been anonymized in unlinkable fashion.

Statistical analysis

A Granger causality test based on a vector auto-regressive (VAR) model was constructed to verify the association between EV-D68 detection and number of asthma hospitalizations, ICU admission and mechanical ventilation support. The model included month as a fixed effect to account for the seasonal effects. Fisher’s exact test was used to compare gender differences in ICU admission and mechanical ventilation support. All significance tests were two tailed. $P$ values of 0.05 or less were considered to indicate statistical significance. All statistical analyses were performed using the SAS software Ver. 9.4 (SAS Institute, Cary, North Carolina, USA.) and R v.3.1.0 software (The R Foundation for Statistical Computing, http://www.r-project.org/).

Results

Time-trend of acute asthma hospitalizations

Data were retrieved from 157 hospitals throughout Japan (excluding Okinawa prefecture, which had not filed any reports). Patients hospitalized with acute asthma exacerbation during the survey period from January 2010 through October 2015 numbered 87,189, and those who needed ICU management and mechanical ventilation numbered 477 and 1,193, respectively. Figure 1 shows the time-trend of asthma exacerbations. The seasonality of hospitalizations is evident from the peaks seen in October of 2010, 2011, 2012 and 2013. However, the peak was exceedingly high in September 2015 (Fig. 1A). Likewise, the numbers of ICU admissions and mechanical ventilation support were very high in September 2015 (Fig. 1B). The time-trend of EV-D68 detection by IDSC shows three peaks, in September 2010, 2013 and 2015, and the peak in 2015 was very high and appeared to coincide with the 2015 asthma exacerbation peak (Fig. 1A–C).

Granger causality test based on VAR model

As seen in Figure 1, asthma hospitalization, mechanical ventilation support and ICU admission appear to have been related to EV-D68 detection. To more accurately assess causality, a Granger causality test was conducted to verify the relationship between asthma events and EV-D68. The null hypothesis that EV-D68 does not Granger-cause hospitalization was rejected with a $P$ value = 0.0013. Therefore, EV-D68 is the Granger cause of asthma hospitalization. EV-D68 was also the Granger cause of mechanical ventilation (Table 1). Because the number of ICU admissions was small, Granger causality could not be demonstrated.

Analysis by age and gender

The time-trend for hospitalizations was analyzed by age group, and significant increases were found in September 2015 in age groups 3–6 and 7–12, but not age groups 1–2 and 13–19 (Fig. 2). Generally, the number of hospitalizations was highest in the 1–2 year-old group, followed by 3–6 years. But in September 2015, the number was highest in the 3–6 year-old group. Generally, more boys were hospitalized than girls, and that trend was also seen in September 2015. However, the numbers of ICU admissions and mechanical ventilations in September 2015 were significantly higher in girls than in boys (Table 2). The odds ratios for risk of ICU admission and mechanical ventilation in girls versus boys were 3.77 and 1.92, respectively ($P$ = 0.002 and $P$ = 0.016).

Analysis by region

To analyze for regional differences in the September “peak”, ratios of hospitalization numbers in September 2015 vs. 2014 were
calculated for each prefecture (Fig. 3). There were regional differences in the ratios, with high ratios seen in the northeast and central regions of Japan. Number of hospitalizations in each prefecture in 2015 is summarized in Supplementary Table 1.

Co-morbid AFP

In 2015, the responding hospitals reported a total of 27 AFP cases, apart from asthma hospitalizations, and only four cases had wheezing.

Discussion

An unusual increase in pediatric asthma hospitalizations in Japan was recognized by many pediatricians in September 2015. Coincidentally, an epidemic of EV-D68 was reported, and the virus was detected in four consecutive cases of severe asthma exacerbation at a large children’s hospital in Tokyo. To investigate the possibility of an epidemiological connection between the two events, namely, asthma exacerbation and EV-D68, we conducted a retrospective nation-wide survey. We determined the time-trends of hospitalizations, ICU admissions and mechanical ventilation support due to acute asthma exacerbation in children during the

![Fig. 1](image.png)

Fig. 1. Time-trends of pediatric asthma hospitalization, mechanical ventilation use for asthma, ICU admission due to asthma, and detection of EV-D68 during the study period from January 2010 through October 2015 in Japan. (A) Number of patients hospitalized for asthma; (B) numbers of asthma patients who needed mechanical ventilation or ICU admission; and (C) number of EV-D68 detections by IDSC in Japan.

Table 1

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Variable</th>
<th>F</th>
<th>df1</th>
<th>df2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of virus detections &gt;10</td>
<td>Hospitalization</td>
<td>5.6212</td>
<td>3</td>
<td>98</td>
<td>0.001345</td>
</tr>
<tr>
<td></td>
<td>MV</td>
<td>5.3149</td>
<td>3</td>
<td>98</td>
<td>0.001952</td>
</tr>
<tr>
<td></td>
<td>ICU</td>
<td>1.8365</td>
<td>3</td>
<td>98</td>
<td>0.1455</td>
</tr>
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</table>

MV, mechanical ventilation; ICU, intensive care unit.
5-year period preceding and including the 2015 EV-D68 epidemic. Those time-trends elucidated that significant peaks of those events occurred in September 2015, in association with EV-D68 detection.

EV-D68, unlike most other enteroviruses, has a predilection for the respiratory tract rather than the gastrointestinal tract because it grows optimally at 33°C, does not tolerate an acidic environment and binds to the α2-6-linked sialic acids found in the respiratory epithelium. It causes a wide variety of respiratory disorders in children, from upper respiratory infections to severe pneumonia and respiratory failure. A recent systematic review summarized the symptoms of EV-D68 infection in 195 children reported in 19 studies. The most common symptom was coughing in 38%, followed by wheezing in 21%, chest indrawing in 15% and breathing difficulty in 13%. As non-respiratory symptoms, fever was the most common symptom, found in 24%, followed by gastrointestinal symptoms in 8% and malaise in 4%. In a 2014 EV-D68 outbreak in California and Colorado, clusters of children with neurological system involvement, namely acute flaccid paralysis (AFP), were reported. Although most of the reports did not describe wheezing as asthma, 83% were treated with albuterol and 56% received systemic corticosteroids during an Arizona outbreak and the basic care plan for the patients in a Kansas outbreak followed the guidelines for asthma with severe bronchospasm, resulting in a favorable outcome. Although it may not be possible to make a clear distinction between asthma exacerbation induced by a virus and wheezing as a manifestation of EV-D68 infection, acute airflow limitation leading to wheezing symptoms is a characteristic feature of EV-D68 infection in children.

In this study, we did not prove a direct causal relationship between EV-D68 and asthma exacerbation, but a Granger causality test showed a statistically significant association between the two parallel events, EV-D68 epidemic and asthma hospitalization. According to the IDSC report (http://www.nih.go.jp/niid/en/), detection rates of EV-D68 in nasopharyngeal samples from children hospitalized with asthma exacerbation in August to October in 2015 in several cities in Japan were 30–40%. One report described positive detection of EV-D68 in eight (73%) of 11 consecutive asthma exacerbation cases in the last week of September and only two (18%) of 11 consecutive cases in the first 2 weeks of October. The other cases were positive for rhinovirus. These findings suggest that EV-D68 was a major “culprit” virus that caused asthma exacerbation in September 2015 in Japan.

Small surges in EV-D68 in 2010 and 2013 did not appear to be related with asthma exacerbation in the corresponding years. Phylogenetic analyses of circulated EV-D68 in the world and in Osaka, Japan showed that multiple clades of the virus emerged and that circulated strains in Osaka were Clade C in 2010, Clade A in 2013 and Clade B in 2015, suggesting that Clade B may be a major contributor to 2015 outbreak in Japan. Clade B was also identified in most isolated strains in 2014 outbreak in North America. Clade B is a newly emerged strain with highly specific alterations in VP1 protein residues, which may have caused significant morbidity in children. Further study is necessary to clarify pathogenic characteristics of the virus strains.

Limitations of this study should be mentioned. First, we were not able to identify the viruses in all cases of asthma hospitalization. However, the urgent public health need for elucidation of EV-D68 activity in Japan, which appeared to cause asthma exacerbation and AFP, necessitated that we perform a retrospective nation-wide survey.

**Table 2**

<table>
<thead>
<tr>
<th>ICU admission</th>
<th>No ICU</th>
<th>ICU</th>
<th>Odds ratio</th>
<th>94% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1696</td>
<td>7</td>
<td>3.77</td>
<td>1.58–9.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>1158</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Mechanical ventilation</th>
<th>No MV</th>
<th>MV</th>
<th>Odds ratio</th>
<th>94% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1677</td>
<td>26</td>
<td>1.92</td>
<td>1.15–3.21</td>
<td>0.016</td>
</tr>
<tr>
<td>Female</td>
<td>1142</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MV, mechanical ventilation; ICU, intensive care unit. * Fisher’s exact test.
in asthma management, can be easily caused by a respiratory infection. For that reason, we hope that our present effort will lead to establishment of a monitoring system for asthma hospitalization that is closely connected with an infectious disease surveillance system. Second, the detailed clinical backgrounds of the patients were not available, since retrieval of the information from over 87,000 cases was impractical. A case registration system is necessary.

In conclusion, we identified a "spike" of acute asthma exacerbation events in September 2015 in Japan and we showed that the spike was associated with an EV-D68 epidemic. A monitoring system for asthma and respiratory infection may be helpful for preventing such two closely related events.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alit.2017.04.003.

Conflict of interest

The authors have no conflict of interest to declare.

Authors’ contributions

TF conceived the study. SK, TF, KM and KO designed the study. SK made significant contributions to acquisition and analysis of the data. YS and KN performed statistical analyses. SK and TF wrote the manuscript. All authors made substantial contributions to the design, collection and interpretation of data. All authors critically reviewed and approved the final manuscript.

References


