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ORIGINAL ARTICLE

Hospitalizations Associated with Pandemic Influenza A (H1N1) 2009 in Asthmatic Children in Japan

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ABSTRACT

Background: The pandemic influenza A (H1N1) 2009 [pdm (H1N1) 2009] spread through the world in 2009, producing a serious epidemic in Japan. Since it was suggested early that asthma is a risk factor for an increased severity of the infection, the Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) organized a working group for countermeasures, and investigated asthmatic children admitted to the hospitals for pdm (H1N1) 2009 infection.

Methods: An appeal was made on the home page of the JSPACI to medical practitioners to input clinical information about asthmatic and non-asthmatic children (0-19 years) admitted to the hospital with pdm (H1N1) 2009 infection.

Results: A total of 862 children (390 with asthma, and 472 without asthma) from 61 medical centers were registered, and the data of 333 asthmatic children and 388 non-asthmatic children in all were entered in the analyses. The mean age was 7.4 ± 2.9 years in the asthma group and 6.9 ± 3.8 years in the non-asthma group. The percentage of children admitted for respiratory symptoms was significantly higher in the asthma group than in the non-asthma group ($p < 0.001$). There was no significant difference in the frequency of admission to the ICU or need for mechanical ventilation support between the two groups. No definite trend was detected in the relationship between the severity of asthma and the intensity of asthma attack. Antiviral drugs were administered within 24 hours in about 85% of the patients in both groups.

Conclusions: Asthma may not be a risk factor for severe pdm (H1N1) 2009 infection in children.

KEY WORDS

asthma, child, pandemic influenza A (H1N1) 2009

INTRODUCTION

The pandemic influenza A (H1N1) 2009 [pdm (H1N1) 2009] infection caused by a new-type influenza virus, derived from crossing of the molecular features of North American and Eurasian swine, avian and human influenza viruses, originated in Mexico in April 2009, and spread rapidly around the world.[1-3] In Japan, the first case of pdm (H1N1) infection was reported in May 2009, although it was not immediately followed by an epidemic; the serious outbreak began in the fall of 2009.

There had been reports from the early phase of the influenza pandemic, that pdm (H1N1) 2009, unlike conventional influenza viruses, causes serious respiratory symptoms and that the infection is often more severe in the younger population, including children.[2,3] And it was also reported that asthma was the most common underlying disease for the infection.[4] Thus, the Japanese Society of Pediatric Allergy and Clinical Immunology, prompted by the necessity to take immediate countermeasures for asthmatic children, started preparation against the pdm (H1N1) 2009 outbreak in August 2009; as a part of this preparation, it began an investigation of asthmatic and non-asthmatic children admitted to the hospital with pdm

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(H1N1) 2009 infection in September 2009. To the best of our knowledge, this is the first report of analysis focused on asthma as one of the most important risk factors for pdm (H1N1) 2009 infection.

METHODS

SUBJECTS

Children (0-19 years) diagnosed to have pdm (H1N1) 2009 infection since April 20, 2009, who satisfied the following 2 conditions:

1) had underlying doctor-diagnosed asthma according to the Japanese guideline for childhood asthma (Japanese Pediatric Guideline for the Treatment and Management of Bronchial Asthma, JPGL) criteria;

2) required hospitalization for respiratory, neurological, or other symptoms.

The control group consisted of non-asthmatic children (who has no history of asthma or no history of wheezing for infants) satisfying condition 2).

Children with the following comorbidities were excluded from the analysis, because the comorbidities could affect the severity of the pdm (H1N1) 2009 infection, or because its differentiation from asthma could be difficult:

Symptomatic epilepsy (2 patients), multiple malformation syndrome (1 patient), leukemia (2 patients, being treated), idiopathic thrombocytopenia (1 patient, being treated), type 1 diabetes (2 patients, being treated), cerebral palsy (3 patients), myopathy (1 patient), tracheostomy (1 patient), nephrotic syndrome (3 patients, being treated), congenital adrenal hyperplasia (1 patient), congenital hydrocephalus (1 patient), juvenile rheumatoid arthritis (1, being treated with tocilizumab), mucopolysaccharidosis (1 patient), trisomy 21 (1 patient), hypoplastic left heart syndrome (1 patient), bronchiectasis (1 patient).

METHODS OF STUDY

An appeal was made on the home page of the Japanese Society of Pediatric Allergy and Clinical Immunology to its members, after informing them about the study, to input replies to the questions posed on the home page. The items requested to be input were, essentially, (1) age, (2) sex, (3) duration of the disease (number of days from onset to admission), (4) reason for admission (chief complaint), (5) occurrence of convulsions during the course of the influenza infection (yes/no), (6) occurrence of signs of encephalopathy during the course of the influenza infection (yes/no), (7) occurrence of dyspnea during the course of the influenza infection (yes/no), (8) time of appearance of dyspnea [if reply to (7) is 'yes'; how many hours after symptom onset was dyspnea felt?], (9) lowest value of SpO_2 (room air), (10) needed admission to ICU (yes/no), (11) needed mechanical ventilation support (yes/no), (12) chest X-ray findings, (13) severity of asthma, (14) treatment step in long-term asthma management, (15) intensity of the asthma attack [(13)-(15) is not applicable for control group]. In addition, the respondents were also requested to enter the laboratory data (white blood cell count, CRP, etc.), content of the treatment, and the outcome.

The data of patients for whom response entries to less than 80% of the essential items had been made, of those whose age was unknown, and of those who were over 20 years of age were excluded from the analysis.

METHODS OF ANALYSIS

Using the chi-square test for frequency data and the t-test for numerical data, the results were compared between the asthma and non-asthma groups. In regard to the time of appearance of dyspnea, when fever was taken to mark the onset of the infection, replies to the question of how many hours it took for the dyspnea to appear after the onset were sometimes given in the negative (because the dyspnea had occurred prior to the onset of fever). Accordingly, we determined that the onset was at 48 hours before fever, event was the appearance of dyspnea, and, if the event did not occur, observation was discontinued for 5 days after the onset of fever, and censored data were compared between the two groups by the Kaplan-Meier method and the log-rank test. As for the relationship between the level of severity of asthma and the intensity of the asthma attack, the level of severity of asthma, based on the clinical features and the current treatment step for asthma, and the intensity of attack were used as categorical variables, and the trend was tested by the Jonckheere-Terpstra test. The significance level in all tests was set at $p < 0.05$. All the statistical analyses were conducted using the SAS 9.2 and JMP 8.0 software.

RESULTS

SUBJECTS OF THE ANALYSIS

There were 862 registered patients (390 with asthma, 472 without asthma) from 61 medical centers, and, after exclusion of the patients who did not fulfill the eligibility criteria and those with deficient data input, finally, a total of 721 patients, including 333 asthmatic patients and 388 non-asthmatic patients, were entered into the analyses. The duration of hospitalization of registered patients was from August 8 to November 27 in 2009. The mean age was 7.4 ± 2.9 years in the asthma group and 6.9 ± 3.8 years in the non-asthma group. Figure 1 shows the age distribution. The percentage of children under 6 years of age was 26% in the non-asthma group and 37% in the asthma group. The male/female ratio was 1.8 : 1.0 in the non-asthma group and 2.1 : 1.0 in the asthma group. There was no significant difference in the male/female ratio between the asthma and non-asthma groups ($p = 0.209$).

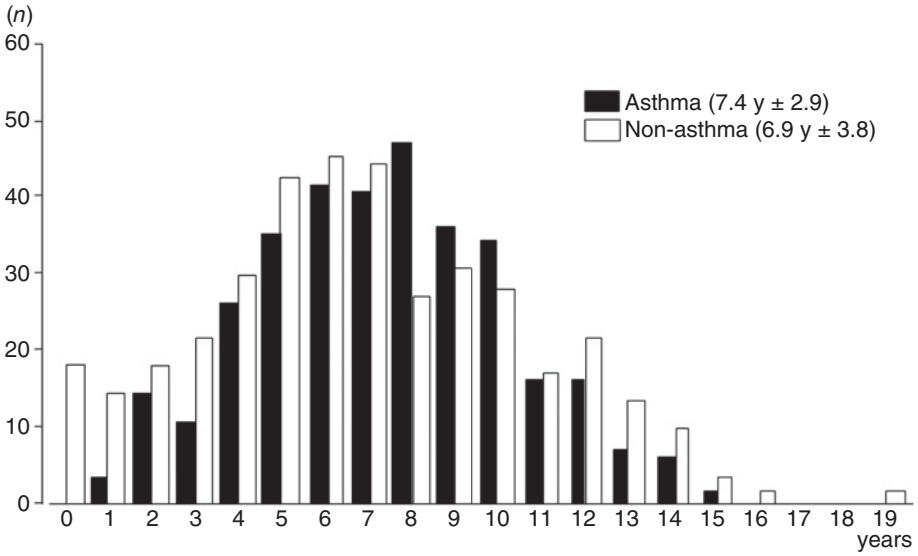

Fig. 1 Age distribution in subjects. The mean age was 7.4 years in the asthma group and 6.9 years in the non-asthma group.

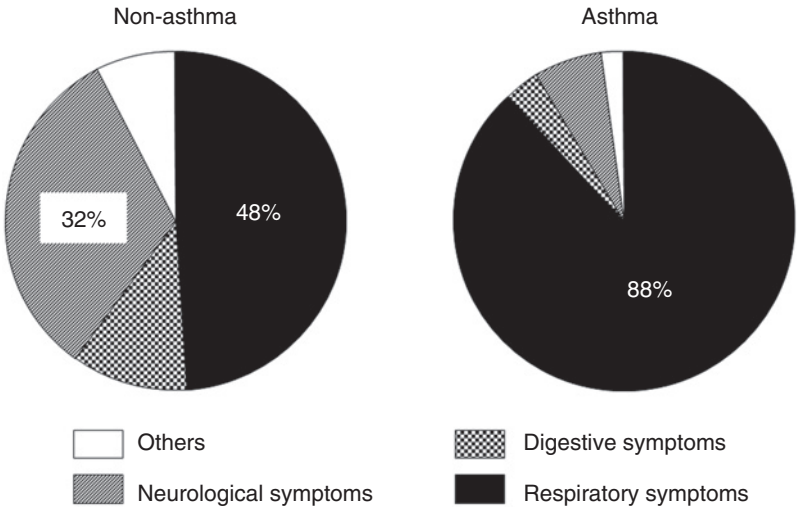

Fig. 2 Reasons for admission: In asthma group, the majority of reasons for admission were respiratory symptoms (88%). In non-asthma group, reasons for admission were respiratory symptoms in 48%, and neurological symptoms in 32%.

REASON FOR ADMISSION

In the asthma group, 88% of the patients were admitted for respiratory symptoms, and in the non-asthma group, 48% were admitted for respiratory symptoms and 32% for neurological symptoms (Fig. 2). The percentage of patients presenting with respiratory symptoms was thus significantly higher in the asthma group than in the non-asthma group ($p < 0.001$).

OCCURRENCE OF CONVULSIONS

During the course of influenza, convulsions occurred in 5% of the patients in the asthma group and 20% of the patients in the non-asthma group (Fig. 3). Statistical comparison between the two groups revealed that the occurence of convulsions was significantly higher in the non-asthma group than in the asthma group ($p < 0.0001$).

OCCURRENCE OF SIGN OF ENCEPHALOPATHY

Encephalopathy was detected in 4% of patients in the asthma group and 4% of patients in the non-asthma group, with no significant difference in the incidence of signs of encephalopathy between the two groups.

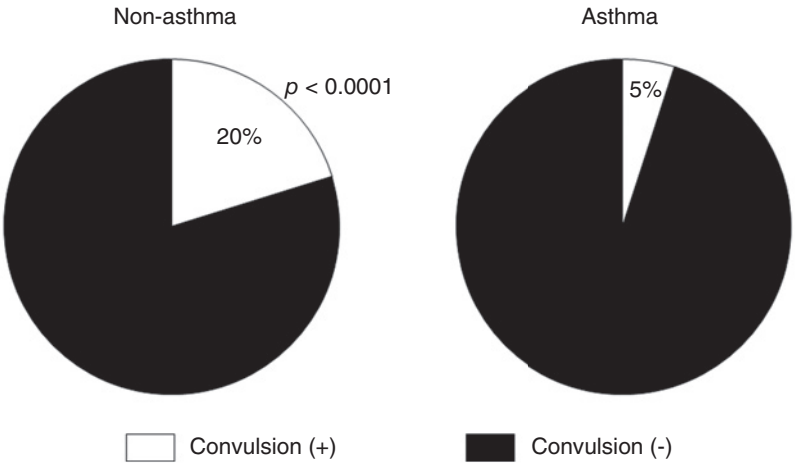

Fig. 3 Occurrence of convulsion. During the course of influenza, convulsions occurred in 5% of the patients in the asthma group and 20% of the patients in the non-asthma group.

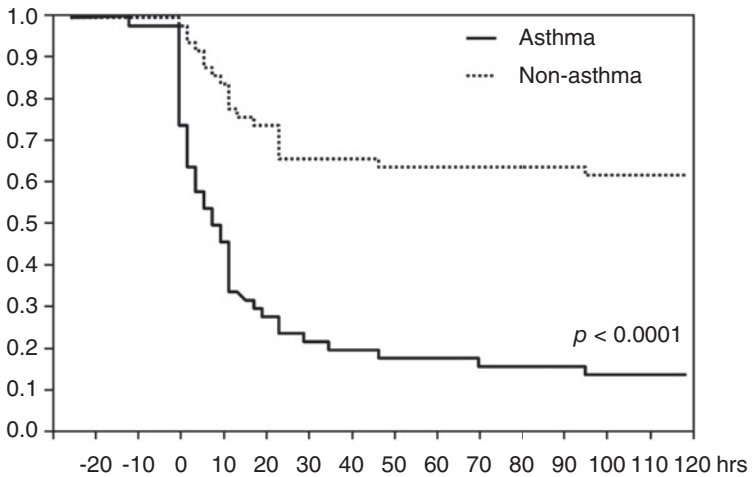

Fig. 4 Time of the appearance of dyspnea. Dyspnea occurred in 36% of non-asthmatics, and the mean time of appearance was 17.9 hours after onset. Dyspnea occurred in 82% of patients with asthma and the mean time was 12 hours. Patients complained of dyspnea significantly earlier in the asthma group.

TIME AND FREQUENCY OF APPEARANCE OF DYSPNEA

Dyspnea occurred in 36.1% of patients in the non-asthma group, and the mean time of appearance of dyspnea in the children who developed dyspnea was 17.9 ± 20.9 hours after the onset. Dyspnea occurred in 82.0% of patients in the asthma group and the mean time of appearance of dyspnea was 12.1 ± 19.9 hours after the onset in the asthma group. When no dyspnea occurred until the end of 5 days' (120 hours) observation after the onset, the reply to the question on the occurrence of dyspnea was 'no' (censored data), and data were analyzed by the Kaplan-Meier method, as shown in Figure 4. It became clear from the results of the log-rank test that patients complained of dyspnea significantly earlier in the asthma group ($p < 0.0001$).

ADMISSION TO THE ICU

Admission to ICU was indicated in 7% of patients in the asthma group and 5% of patients in the non-asthma group, with no significant difference in the frequency of ICU admission between the two groups.

NEED FOR MECHANICAL VENTILATION SUPPORT

Mechanical ventilation support was needed in 4% of patients in the asthma group and 1% of patients in the

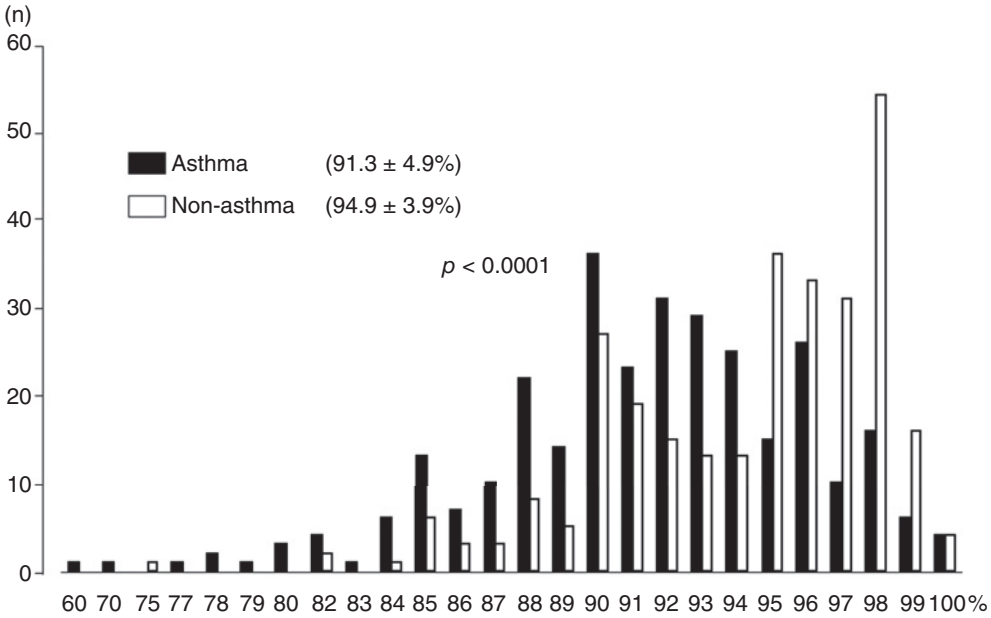

Fig. 5 The SpO2 on room air at admission was 91.3% in the asthma group and 94.3% in the non-asthma group.

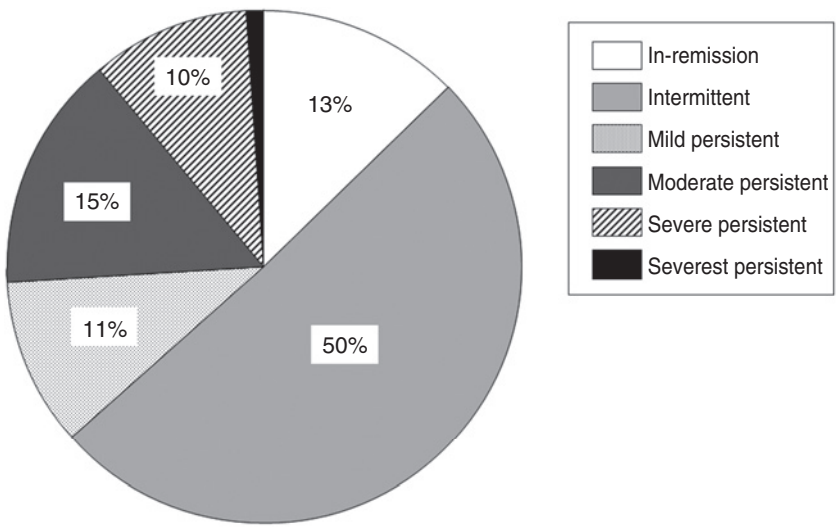

Fig. 6 Severity of asthma: the severity based on the clinical features and the current treatment step for asthma. The in-remission and intermittent type accounted for 63% of asthma group.

non-asthma group, with no significant difference between groups in this respect.

SpO_2

The minimum value of SpO_2 on room air during admission was 91.3 ± 4.9% in the asthma group and 94.3 ± 3.9% in the non-asthma group (Fig. 5). Statistical comparison between the two groups revealed that SpO_2 during admission was significantly lower in the asthma group ($p < 0.0001$).

SEVERITY OF ASTHMA

In terms of the level of severity of asthma assessed based on the clinical features and the current treatment step for asthma in the asthma group, the in-remission and intermittent types were the most frequent (together accounting for 63% of all the cases) (Fig. 6).

INTENSITY OF ASTHMA ATTACK

There was no acute asthma attack in 35% of the pa-

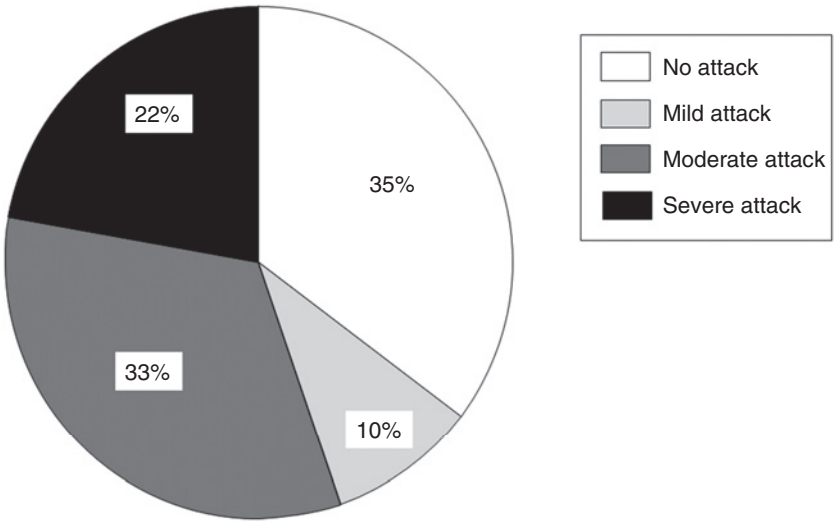

Fig. 7 Intensity of asthmatic attack: No attack 35%, mild 10%, moderate 33%, severe 22%.

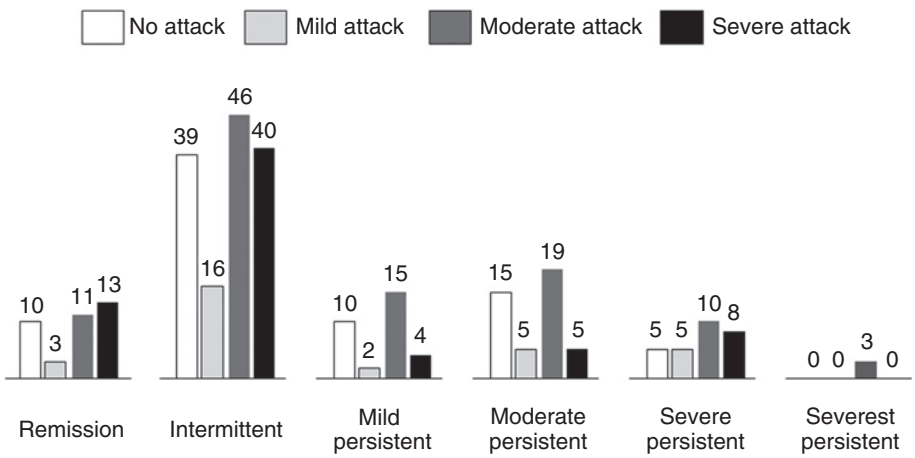

Fig. 8 Relationship between the severity of asthma and the intensity of attack: No definite trend was detected by Jonckheere-Terpstra test.

tients, with asthma attacks occurring in 65% of all the patients in the asthma group (Fig. 7).

RELATIONSHIP BETWEEN THE SEVERITY OF ASTHMA AND THE INTENSITY OF THE ASTHMA ATTACK

No definite trend was detected in the intensity of the asthma attack in the 6 groups classified according to the asthma severity (in-remission to severe persistent type) by the Jonckheere-Terpstra test (Fig. 8).

ANTIVIRAL MEDICATION

The mean interval time from the appearance of symptoms to the initiation of antiviral drug administration was 19.7 hours in the non-asthma group and 16.2 hours in the asthma group. Antiviral medication was started within 24 hours of the onset in about 85% of all the children in both groups.

DISCUSSION

Data from the American continent, where the pdm (H1N1) 2009 epidemic had already occurred before it arrived in Japan, suggested that asthma was the most common underlying disease seen in both children and adults infected with the virus.[4] Accordingly, the working group of the Japanese Society of Pediatric Allergy and Clinical Immunology conducted a survey of the actual status of pdm (H1N1) 2009 infection in Japan from September 2009, and performed analyses from the standpoint of various factors related to asthma.

Subjects of this analysis were mainly children diagnosed to have influenza A by the influenza virus antigen test performed on nasal swab samples using a

rapid diagnosis kit, and not all the children were diagnosed by the PCR test. However, about 98% of the isolates were the pdm (H1N1) 2009 virus strain during the influenza season from 2009 through 2010 in Japan, and the seasonal influenza viruses that had caused the epidemic until then were scarcely isolated.[5] Thus, it may be assumed that almost 100% of the subjects of the present study were infected with the pdm (H1N1) 2009 influenza virus.

In this research, we included infants and toddlers with recurrent wheezing in the analysis as 'asthmatic children', because we consider such young children with recurrent wheezing as asthma, if they experienced 3 or more independent episodes of wheezing/dyspnea after ruling out other associated diseases such as obstructive airway diseases, chronic lung disease, according to JPGL.[6]

Since all subjects of the present study were hospitalized, the influenza virus infection may be assumed to have been moderate to severe. Age distribution showed no bias towards infants or young children. This tendency was in agreement with that reported by the U.K. study.[7] An interesting finding was obtained with respect to the sex distribution, with the frequency being about twice as high in boys as in girls. Although the cause for this difference in the sex predilection is not clear, the sex ratio reported from most other countries is 1 : 1.[4,7] Further studies are awaited on this issue.

In the study of November 2009 in Japan, asthma was the most common underlying disease found in 27% of the 220 patients with severe pneumonia caused by pdm (H1N1) 2009 infection, roughly the same percentage as that reported from the U.S.[8] One of the major questions at the beginning of the pandemic was very simple: "Is the new-type influenza infection exacerbated in correlation with the severity of asthma?" To this question, the results of the present study suggested a negative answer. The severity of the underlying asthma was classified as the in-remission to mild intermittent type in 63% of the patients, mild persistent type in 11%, moderate persistent type in 15%, severe persistent type in 10% and severest persistent type in 1% of the hospitalized patients. This tendency was not significantly different from that in all children with asthma in Japan[9] (data in Japanese). And the analysis of the relationship between the severity of asthma and the intensity of acute asthma attack revealed that no definite trend was detected among the 6 groups classified according to the severity of the asthma (Fig. 8). Based on the above findings, it would be difficult to assume the severity of asthma as a factor influencing the severity of pdm (H1N1) 2009 virus infection.

Dyspnea occurred earlier and more in the asthma group than in non-asthma group. However, no significant differences were seen between groups in the frequency of ICU admission or mechanical ventilation, which suggests that asthma may not be a risk factor for severe pdm (H1N1) 2009 infection in children. In patients with pdm (H1N1) 2009 infection enrolled in a U.K. study, asthma was the most common underlying medical condition. However, in an analysis of patients with serious infection, the severity of the infection was not related with the presence of underlying asthma.[7] Also in a Singapore study, asthma was a significant risk factor for hospitalization by pdm (H1N1) 2009 infection. However, in the serious cases, no significant correlation was found.[10]

Convulsion during the course of the influenza infection occurred more frequently in the non-asthma group, contrary to our expectation (5% vs. 20%; Fig.4). According to past bibliographic data, no specific association was detected between asthma and the incidence of seizures.[11] And an influence of sampling bias would be involved. Thus, further study is necessary about the more frequent occurrence of convulsions in the non-asthma group observed in the present study.

The present analysis drew our attention to the proactive administration of antiviral drugs to the patients with pdm (H1N1) 2009 infection. In an Argentine study, 17% of hospitalized children needed mechanical ventilation support and 5% died, and antiviral drugs were administered within 24 hours after the onset of symptoms to only 13% of these patients.[12] There were no deaths in our present case series. In a WHO report, the mortality rate (deaths per million population) associated with pdm (H1N1) 2009 was 0.2 as of November 6, 2009 in Japan, the lowest among 11 countries, including Canada, U.K., Mexico, U.S., South Africa, Argentina, Australia, Brazil, Chile, and New Zealand (1.8-14.6).[13] Multiple factors may be involved in this difference in the prognoses, which were also varied, making reasonable comparison difficult. However, it would be difficult to rule out the possibility that proactive administration of antiviral drugs improved the prognosis of pdm (H1N1) 2009 infection as a whole, including that in asthmatic children, in Japan. For the cases analyzed above, systemic corticosteroids were used for severe respiratory symptoms in about 76% of asthmatics, 58% in non-asthmatics. Since the utility of systemic corticosteroid therapy for moderate to severe cases affected by pdm (H1N1) 2009 is still controversial,[14,15] further studies are required.

To summarize, there is scarce evidence to suggest that asthma is a risk factor for severe pdm (H1N1) 2009 infection. Asthma itself will have to be controlled on an appropriate long-term schedule. In the presence of pdm (H1N1) 2009 infection, antiviral medication from an early phase may be considered, regardless of the presence or absence of underlying asthma.

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