

Characteristics of atopic children with pandemic H1N1 influenza viral infection: Pandemic H1N1 influenza reveals 'occult' asthma of childhood

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The number of human cases of pandemic H1N1 influenza viral infection has increased in Japan since April 2009, as it has worldwide. This virus is widespread in the Yamaguchi prefecture in western Japan, where most infected children exhibited respiratory symptoms. Bronchial asthma is thought to be one of the risk factors that exacerbate respiratory symptoms of pandemic H1N1-infected patients, but the pathogenesis remains unclear. We retrospectively investigated the records of 33 children with pandemic H1N1 influenza viral infection who were admitted to our hospital between October and December 2009 and analyzed their clinical features. The percentage of children with asthma attack, with or without abnormal findings on chest radiographs (pneumonia, atelectasis, etc.), caused by pandemic H1N1 influenza infection was significantly higher than that of children with asthma attack and 2008–2009 seasonal influenza infection. Of the 33 children in our study, 22 (66.7%) experienced an asthma attack. Among these children, 20 (90.9%) did not receive long-term management for bronchial asthma, whereas 7 (31.8%) were not diagnosed with bronchial asthma and had experienced their first asthma attack. However, the severity of the attack did not correlate with the severity of the pulmonary complications of pandemic H1N1 influenza viral infection. The pandemic H1N1 influenza virus greatly increases the risk of lower respiratory tract complications such as asthma attack, pneumonia, and atelectasis, when compared to the seasonal influenza virus. Furthermore, our results suggest that pandemic H1N1 influenza viral infection can easily induce a severe asthma attack, pneumonia, and atelectasis in atopic children without any history of either an asthma attack or asthma treatment.

Human cases of the pandemic H1N1 influenza viral infection were first reported in patients from Mexico and the United States in early April 2009; this infection subsequently spread worldwide, including Japan. Since September 2009, the number of pandemic H1N1 influenza cases has dramatically increased in many areas of Japan, including the Yamaguchi prefecture. In a ferret model, the pandemic H1N1 influenza virus has been reported to more extensively replicate than the seasonal H1N1 influenza virus in parts of the lower respiratory tract such as the trachea and bronchioles (1). Most patients with pandemic H1N1 viral infection exhibit respiratory symptoms. Some studies have shown that certain risk factors such as respiratory disease, cardiac disease, and renal failure may increase mortality; further, bronchial asthma, in particular, is thought to be one of the risk factors that exacerbate respiratory symptoms (2, 3). However, the asso-

ciation of bronchial asthma with the pathogenesis of pandemic H1N1 influenza viral infection remains unclear.

Thus, in this study, to evaluate the relationship of bronchial asthma with this infection, we retrospectively analyzed the clinical features of children with pandemic H1N1 influenza viral infection who were admitted to our hospital between October and December 2009.

Patients and methods

Patients

This study included children with pandemic H1N1 influenza viral infection who were admitted to the Department of Pediatrics, Yamaguchi University Hospital between October and December 2009; these children were diagnosed using the immunochromatographic assay method (Quick chaser Flu A,

B; Mizuho Medy Co. Ltd., Saga, Japan) and/or polymerase chain reaction (PCR) with epithelial cells of the nasal cavity. One child was diagnosed with this infection on the basis of family history. We diagnosed the patients with bronchial asthma attack on the basis of wheezing in the chest, complications associated with other allergic diseases such as allergic rhinitis or atopic dermatitis, and effectiveness of anti-asthmatic medicines such as β_2 agonists and corticosteroids, according to the Japanese Pediatric Guidelines for the Treatment and Management of Bronchial Asthma 2008 (JPGL 2008) (4, 5). In addition, we excluded patients with cardiovascular diseases or anomalies. We also determined the severities of bronchial asthma and asthma attacks according to JPGL 2008 (4, 5). The severity of the asthma attack at admission was as follows: mild attack, moderate attack, severe attack, and respiratory failure. Further, the severity of bronchial asthma at admission was as follows: intermittent, mild persistent, moderate persistent, and severe persistent.

Study design

We compared the clinical features of children with pandemic H1N1 influenza infection with those of children with 2008–2009 seasonal influenza infection who were admitted to our hospital from December 2008 to April 2009. Among the children belonging to the pandemic H1N1 influenza viral infection group, we also compared the clinical features between the asthma attack and non-asthma attack subgroups. Furthermore, we analyzed the characteristics of the patients who experienced an asthma attack during the pandemic H1N1 influenza viral infection.

Determination of serum levels of IgE and antigen-specific IgE

Serum levels of total IgE and antigen-specific IgE were determined using fluorescence enzyme immunoassay methods at SRL Inc. (Tachikawa, Tokyo, Japan).

Statistical analysis

Differences in the results of the two groups were analyzed using Student's *t*-test and χ^2 test; a *p* value <0.05 was regarded as statistically significant. The analyses and calculations were performed using the Statistical Package for Social Sciences (SPSS)-12.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 presents the clinical profiles of the children with pandemic H1N1 infection and 2008–2009 seasonal influenza infection who were admitted to the Department of Pediatrics, Yamaguchi University Hospital. The percentage of children with bronchial asthma attacks and pneumonia or atelectasis, as determined on the basis of abnormal findings on the chest radiographs, in the pandemic H1N1 influenza infection group was significantly higher than that in the 2008–2009 seasonal influenza infection group (*p* = 0.002 and *p* < 0.001, respec-

Table 1 Comparison of clinical characteristics between pandemic H1N1 influenza patients and 2008–2009 seasonal influenza patients

	Pandemic H1N1	2008–2009 seasonal	<i>p</i> value
Number	33	17	
Sex (M:F)	24:9	10:7	0.354
Age (years)	5.2 ± 4.0	3.3 ± 3.6	0.122
Asthma attack	22 (66.7%)	2 (11.8%)	<0.001
Croup	0 (0.0%)	2 (11.8%)	0.048
Abnormal chest x-ray	16 (48.5%)	1 (5.9%)	0.002
Febrile convulsion	7 (21.2%)	7 (41.2%)	0.155
Abnormal behavior	2 (6.1%)	0 (0.0%)	0.293
Dehydration	2 (6.1%)	1 (5.9%)	0.502

tively). On the other hand, the percentage of children with croup in the seasonal influenza infection group was significantly higher than that in the pandemic H1N1 influenza infection group (*p* = 0.048).

Table 2 shows the comparison between the clinical features of the 33 children with pandemic H1N1 influenza with and without a bronchial asthma attack. In both the groups, the children with pandemic H1N1 influenza viral infection were similarly diagnosed using a quick test (asthma attack group, 20/21 [95.2%]; non-asthma attack group, 10/11 [90.9%]) and/or PCR (asthma attack group, 19/19 [100%]; non-asthma attack group, 10/10 [100%]). Of these 33 children, 22 (66.7%) experienced an asthma attack, whereas the remaining 11 (33.3%) did not. In accordance with the results of a previous report, the average age of children with pandemic H1N1 influenza viral infection was higher than that of children with seasonal influenza viral infection, but this difference was not significant (3). In the case of children in the asthma attack subgroup, the C-reactive protein levels were high and the average SpO₂ levels were low on admission, when compared to those in the case of children in the non-asthma attack group. In addition, the mean duration of hospitalization of children in the asthma attack group was longer than that of children in the non-asthma attack group.

Table 2 Clinical characteristics of patients infected with the pandemic H1N1 influenza virus, with and without an asthma attack

	Asthma attack (+)	Asthma attack (–)	<i>p</i> value
Diagnosis of Flu			
PCR	19/19	10/10	–
Quick test	20/21	10/11	0.631
Sex (M:F)	16:6	8:3	1.000
Age (years)	6.0 ± 3.0	3.7 ± 0.8	0.132
Body temperature (°C)	38.4 ± 1.2	38.5 ± 1.0	0.896
SpO ₂ (%)	90.0 ± 3.2	98.2 ± 1.3	<0.001
WBC (/mm ³)	11,478 ± 5,800	10,085 ± 4,198	0.564
CRP (mg/dl)	3.7 ± 2.8	0.4 ± 0.2	<0.001
Duration of admission (days)	8.2 ± 2.1	3.7 ± 2.7	<0.001

Table 3 Clinical characteristics of asthma attack patients with pandemic H1N1 influenza viral infection

Age, sex	Flu diagnosis	Severity of attack	Severity of asthma	Past history of asthma	Long-term management	Duration from last wheeze	IgE (IU/l)	Specific IgE (class)	Chest X-ray pneumonia/atelectasis	Treatment	Others
1 10, M	+/+	Severe	Intermittent	+	–	>5 yr	333	0	+/-	ICU, mPSL, Iso	
2 8, M	+/+	Mild	Intermittent	+	–	1.5 yr	Not tested	Not tested	-/-	mPSL	Febrile convulsion
3 11, F	+/+	Severe	Intermittent	+	–	1 month	2770	House dust 6, mite 6, dog 1	-/-	ICU, mPSL, Iso	
4 3, F	+/+	Severe	–	–	–	–	638	0	+/-	mPSL, Iso	
5 6, F	+/+	Severe	Intermittent	+	–	1 month	376	House dust 4, mite 4	+/-	ICU, mPSL, Iso	
6 10, M	+/+	Severe	Intermittent	+	–	1 yr	156	Cedar 2, hinoki 1, Orchard Grass 1	-/-	ICU, mPSL, Iso, Amy	
7 1, F	Family history	Severe	Intermittent	+	–	1 month	1400	Egg white 1, milk 2	-/-	mPSL, Iso	
8 6, M	+/+	Severe	Intermittent	+	–	1 yr	656	House dust 6, mite 5, cedar 2	+/-	ICU, mPSL, Iso	
9 11, M	+/+	Respiratory failure	–	–	–	–	705	Cedar 6, hinoki 3, cat 3, Canada goldenrod 2, dog 1, vernal grass 1, house dust 1	+/+	ICU, MV, mPSL, Iso, bronchoscopy	Plastic bronchitis
10 9, M	+/+	Severe	–	–	–	–	2540	House dust 6, mite 6, cedar 2, shrimp 2, dog 1	+/-	ICU, mPSL, Iso	
11 6, M	+/+	Severe	Intermittent	+	–	1 yr	4210	House dust 6, mite 6, cedar 3, hinoki 2, dog 1	+/+	mPSL, Iso	
12 1, F	+/not tested	Moderate	Moderate persistent	+	+	1 month	42	0	+/-	mPSL, Iso	VSD, cerebral paralysis
13 0, M	+/+	Moderate	Severe persistent	+	+	1 month	23	Milk 1	+/-	mPSL	
14 5, M	+/+	Moderate	Intermittent	+	–	1 yr	Not tested	Not tested	-/-	mPSL	
15 6, M	+/+	Severe	Intermittent	+	–	2 yr	165	House dust 4, mite 4	+/+	mPSL, Iso	
16 9, M	+/+	Severe	–	–	–	–	856	House dust 2, mite 2, cedar 3, hinoki 3, cat 2, Alternaria 1	+/-	mPSL, Iso	
17 5, M	+/+	Severe	–	–	–	–	926	House dust 5, mite 5, cedar 4, ragweed 3, Orchard Grass 2, wheat 1	+/+	mPSL	
18 4, M	-/+	Severe	–	–	–	–	205	House dust 2, mite 3	+/+	mPSL, Iso	
19 3, F	+/+	Severe	Intermittent	+	–	2 months	936	House dust 5, mite 5, Can-dida 2, egg white 2	+/-	mPSL, Iso	
20 4, M	+/+	Severe	Intermittent	+	–	1 month	1260	House dust 6, mite 6	+/-	mPSL, Iso	
21 5, M	+/+	Severe	–	–	–	–	122	Vernal grass 1	+/+	mPSL, Iso	
22 8, M	+/not tested	Severe	Intermittent	+	–	1 yr	7010	House dust 6, mite 6, cedar 3, dog 2, cockroach 2	-/-	mPSL, Iso	

ICU, intensive care unit; MV, mechanical ventilation; mPSL, methylprednisolone; Iso, continuous isoproterenol inhalation; Amy, Aminophylline; VSD, ventricular septal defect.

On the other hand, the mean body temperature and the average white blood cell (WBC) count in the peripheral blood on admission were similar for the two groups.

Table 3 presents the clinical features of the 22 children with asthma attack belonging to the pandemic H1N1 influenza viral infection group. Fifteen (68.1%) of the 22 children were previously diagnosed with bronchial asthma. These 15 patients had never been admitted to a hospital during the 2008–2009 influenza season. Of the 22 children, only 2 (9.1%) received long-term management for bronchial asthma. The severities of asthma attacks were as follows: mild, 1 patient (4.5%); moderate, 3 patients (13.6%); severe, 17 patients (77.3%); and respiratory failure, 1 patient (4.5%). Of the 15 children with bronchial asthma, 8 (53.3%) had experienced an asthma attack more than a year before admission. Further, 7 children (31.8%) required management in the intensive care unit (ICU), of which patient no. 9 developed respiratory failure caused by bronchial asthma attack and plastic bronchitis; this patient required mechanical ventilation (MV) and bronchoscopy in the ICU. All the children were treated with oseltamivir and methylprednisolone (mPSL) with or without continuous isoproterenol inhalation; this treatment improved the symptoms of all the children, including the one with respiratory failure.

Table 3 presents the levels of serum IgE that were elevated in all the children examined. Data for two children were not available. Table 4 presents the antigen-specific IgE levels; the serum levels of house dust- and mite-specific IgE were elevated in the case of 13 (65.0%) and 12 (60.0%) children, respectively. The levels of IgE against various antigens (except house dust and mite) such as food, cedar pollen, fungus, and animal hair were also elevated in the case of 5 children (25.0%). As shown in Table 3, 3 children (15.0%) did not exhibit an elevation in the levels of IgE specific for the common antigens tested. Sixteen children (72.7%) exhibited pneumonia or atelectasis, as determined on the basis of abnormal findings on the chest radiographs.

Discussion

Studies that examined the characteristics of patients with pandemic H1N1 influenza viral infection (2, 3, 6) suggested that bronchial asthma is one of the risk factors that worsen

respiratory conditions of patients during pandemic H1N1 influenza viral infection. However, the relationship of bronchial asthma with the pathogenesis of pandemic H1N1 influenza viral infection remains unclear. In this study, we retrospectively investigated the characteristics of children who experienced bronchial asthma attack during pandemic H1N1 influenza viral infection and were admitted to our hospital. The percentage of children with abnormal findings on chest radiographs that indicated pneumonia and/or atelectasis was significantly higher in the pandemic H1N1 influenza viral infection group (48.5%) than in the 2008–2009 seasonal influenza viral infection group (5.9%) ($p = 0.002$). This finding may be attributable to the more extensive replication of the pandemic H1N1 influenza virus than that of the seasonal influenza virus in the lower respiratory tract, as previously reported (1). The results of our previous study, which revealed the characteristics of all the children with asthma attacks admitted to our hospital, were as follows: mild attack, 9.7%; moderate attack, 75.7%; severe attack, 14.3%; and respiratory failure, 0.3% (7). Among the children with pandemic H1N1 influenza viral infection and asthma attack in this study, a significantly high percentage of children experienced a severe attack (77.3%); therefore, we suggest that pandemic H1N1 influenza viral infection is more likely to induce a severe asthma attack than are other infections or allergens. Surprisingly, our results show that 20 (90.9%) of the 22 children with pandemic H1N1 influenza viral infection and asthma attack had not received long-term management for bronchial asthma. In addition, our results show that 7 children (31.8%) who were not previously diagnosed with bronchial asthma experienced an attack this time. The serum levels of IgE in the case of all the children examined were elevated. In the case of 17 (85.0%) of the 20 children, the levels of IgE specific to various antigens were elevated. The serum levels of house dust- and/or mite-specific IgE were elevated in the case of 13 (65.0%) and 12 children (60.0%), respectively. Further, 13 patients (59.1%) exhibited intermittent, one patient (4.5%) exhibited moderate persistent, and one patient exhibited severe persistent bronchial asthma. As shown in Table 3, the duration between the current and last asthma attack was long; 9 children (40.9%) experienced the previous attack over a year before admission. These results suggest that an asthma attack induced by pandemic H1N1 influenza viral infection was not correlated with the severity of bronchial asthma. Further, atopic children with high serum IgE levels, with or without high levels of antigen-specific IgE, and without a history of asthma or long-term management of asthma, may also be at a risk for severe asthma attack induced by pandemic H1N1 influenza infection. Taken together, our results show that pandemic H1N1 influenza viral infection could induce severe asthma attack in children who had never been diagnosed with bronchial asthma or who had long durations of non-asthma attack, over 1 yr before admission. We concluded that pandemic H1N1 influenza viral infection may reveal 'occult asthma' although the mechanisms remain unclear. Patients with atopic dermatitis have been shown to exhibit low natural killer cell activity (8–10). We speculate that both, an abnormality of the innate

Table 4. Serum antigen-specific IgE levels in asthma attack patients during pandemic H1N1 influenza viral infection

	n = 20 (%)
House dust	13/20 (65)
Mite	12/20 (60)
Cedar	8/20 (40)
Dog hair	5/20 (25)
Hinoki	4/20 (20)
Cat hair	2/20 (10)
Orchard grass	2/20 (10)
Egg white	2/20 (10)
Milk	2/20 (10)

immunity in atopic individuals and affinity of the pandemic H1N1 influenza virus to the respiratory tract, may lead to the induction of a severe asthma attack during pandemic H1N1 influenza viral infection. These speculations are important, but they are not enough to draw conclusions. A larger sample population of patients with asthma attacks during pandemic H1N1 influenza viral infection needs to be studied to further elucidate the role played by bronchial asthma in exacerbating respiratory symptoms of these patients.

Patient no. 9 exhibited respiratory failure caused by severe asthma attack and plastic bronchitis and thus required MV and bronchoscopy in the ICU. Plastic bronchitis is a rare disease characterized by the formation of large gelatinous or rigid branching airway casts and is usually observed as a complication with specific conditions such as bronchial asthma and cyanotic chronic heart disease and with conditions that develop after a heart surgery (11, 12). To our knowledge, this is the first study that revealed that influenza viral infections caused by both pandemic H1N1 and seasonal influenza virus induce plastic bronchitis. Thus, timely diagnosis and treatment of patients with plastic bronchitis is important.

On the basis of the results of our study, we speculate that untreated asthmatic children may be at a high risk, when compared with children who receive long-term asthma management; however, we were unable to conclude this possibility. The limitation of our study is that we only investigated the clinical reports of children with pandemic H1N1 who were admitted to our hospital. There is a need to assess outpatients with pandemic H1N1 infection. We propose that it is necessary to adequately evaluate the severity of asthma, and that adequate long-term treatment for asthmatic patients must decrease the risk of severe asthma attack induced by pandemic H1N1 influenza viral infection according to the severity of asthma.

In conclusion, our study elucidated that pandemic H1N1 influenza viral infection can easily induce a severe asthma attack and pneumonia and/or atelectasis in atopic children without any history of either asthma attack or asthma treatment. Our results also suggest that the severity of bronchial asthma does not correlate with the severity of asthma attack, pneumonia, or atelectasis induced by pandemic H1N1 influenza viral infection.

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