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대유행 인플루엔자(H1N1 2009) 초기에 소아 호흡기 감염의 임상특징

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Clinical Characteristic of Respiratory Tract Infections in Children during Pandemic Influenza (H1N1 2009) in Korea

Background: Since initial emergence on pandemic influenza (H1N1 2009) in Mexico on March 2009, the first case of pandemic influenza (H1N1 2009) occured on 2 May 2009 in Korea. We describe the clinical characteristics of childhood patients from pandemic influenza (H1N1 2009) and other concurrent respiratory pathogens during early phase of the pandemic influenza in Korea.

Materials and Methods: We have retrospectively studied 959 patients under age of 15 years who have visited Department of Emergency Medicine for a diagnostic test of pandemic influenza (H1N1 2009) or treatment of flu-like illness between May and September of 2009. The pandemic influenza (H1N1 2009) was detected via real-time RT-PCR and other respiratory viruses were detected via multiplex RT-PCR.

Results: A total of 959 patients visited Department of Emergency Medicine at Severance Hospital. Of them, 562 were tested; 124 (12.7%) were positive for pandemic influenza (H1N1 2009). Confirmed patients of pandemic influenza (H1N1 2009) were relatively older than non-H1N1 patients (7.5 years of age vs 4.6 years, $P<0.001$). Among histories or symptoms of patients with flu-like illness, contact history (80%) with another patient with pandemic influenza (H1N1 2009) was an important clue of the infection in early phase of pandemic. Comparing with hospitalized patients with respiratory tract infections due to other causes, lower ESR (32.9±23.5 mm/hour vs 11.5±9.2 mm/hour), hyperkalemia (4.2±0.3 mmol/L vs 5.2±3 mmol/L) and hyponatremia (137.2±2.5 mmol/L vs 124±40.5 mmol/L) were significant laboratory finding and higher cholesterol and GTP were noticed in pandemic influenza (H1N1 2009). Ten confirmed patients with pandemic influenza (H1N1 2009) were hospitalized due to pneumonia and all of them were resolved without any complication.

Conclusions: Respiratory tract infections were caused not only by pandemic influenza (H1N1 2009) virus but also various respiratory viruses. Hospitalized patients, confirmed as pandemic influenza (H1N1 2009), showed a good prognosis. Age and contact history were distinct features and could be an important clue to differentiate causes in patients with febrile respiratory symptoms.

Key Words: Children, Pandemic influenza (H1N1 2009) virus, Korea, Respiratory tract infection

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Introduction

In March 2009, there was an outbreak of human respiratory disease in Mexico, cause of which was identified as a novel swine-origin pandemic influenza (H1N1 2009) virus (S-OIV) (1). In California, S-OIV was also found in the school-aged children (2). In early June 2009, the World Health Organization (WHO) declared the outbreak of pandemic influenza (H1N1 2009) to be a pandemic. As of September 20, 2009, there were over 15,160 confirmed cases of pandemic (H1N1) 2009 influenza; and 9 deaths had been reported in Korea. Of them 53% were aged between 10 and 19 years old and 21% between 20 and 29 years old, which indicate the predominant occurrences of novel influenza viral infection in young adults (3).

Reports in early phase of the Northern hemisphere said that most confirmed cases of pandemic influenza (H1N1 2009) have been self-limited and uncomplicated respiratory disease although some patients have been ill of hospitalized with more severe symptoms and some with increasing mortalities (1, 2, 4, 5). There was a report in Australia and New Zealand which had experienced pandemic influenza (H1N1 2009) in winter season saying that the critical illness had happened in infants and young adults (6). Children experienced more frequently the respiratory infections of various viruses or pathogens in winter season than in warmer seasons. The clinical symptoms of pandemic influenza (H1N1 2009) had been similar to those infected with seasonal influenza and other viruses.

In this report, we described the clinical characteristics of childhood patients showing febrile respiratory illness from pandemic influenza (H1N1 2009) or from other respiratory pathogens during early phase of the pandemic in Seoul, Korea.

Materials and Methods

We retrospectively studied patients under age of 15 years who visited Department of Emergency Medicine for a diagnostic test of pandemic influenza (H1N1 2009) or treatment of flu-like illness between May and September of 2009. The suspicious pandemic influenza (H1N1 2009) was defined as flu-like illness in this period with fever of over 37.8 degrees and respiratory symptoms including cough, rhinorrhea or nasal congestion.

Laboratory diagnosis of pandemic influenza (H1N1 2009) was made by probe-based RT PCR (Roche®, Germany) of nasopharyngeal swab (7). We also performed multiplex RT-PCR (Solgent®, Korea) using the nasopharyngeal aspiration samples. This test was done to identify other respiratory viral pathogens in hospitalized patients who had not been tested or have been ruled out for pandemic influenza (H1N1 2009) for their respiratory infection such as pneumonia, bronchiolitis, croup, asthma and acute respiratory distress syndrome during the same period (8). The target viruses were adenovirus, parainfluenza virus type 1, type 2 and type 3, respiratory syncytial virus, influenza A and B virus, coronavirus, rhinovirus, and bocavirus. Those patients diagnosed as influenza A virus were reconfirmed as seasonal influenza A virus by sequencing.

We analyzed clinical characteristics of patients population who was done a diagnostic test a diagnostic test and compared features of these patients. Also, we showed various respiratory viral pathogens detected during the same period. We also described progress and treatments for inpatients with pandemic influenza (H1N1 2009).

Characteristics of patients are analyzed by frequency, and chi-square test.

Results

1. Characteristics of study population

Between May and September 2009, 959 patients under age of 15 years visited hospital for a diagnostic test of pandemic influenza (H1N1 2009) or treatment of flu-like illness (Fig. 1). Of them, 519

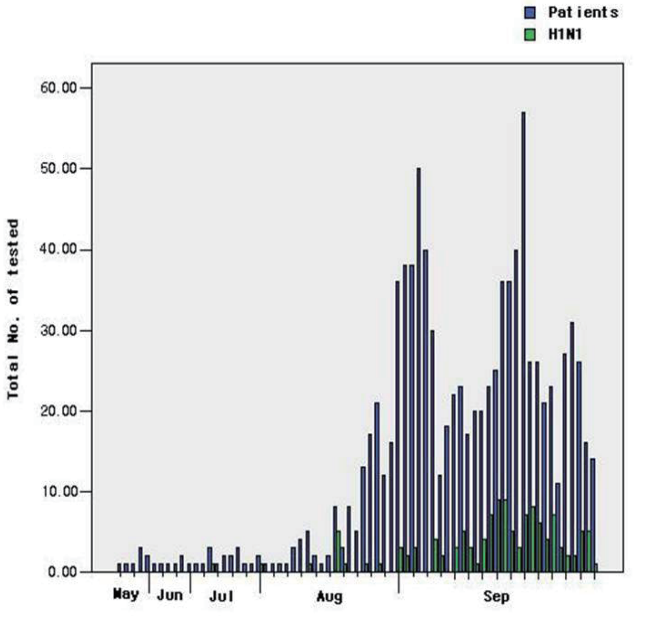

Figure 1. The number of patients with flu-like illness increases in warm and hot seasons and that of confirmed pandemic influenza (H1N1 2009) cases increases simultaneously. H1N1, pandemic influenza (H1N1 2009)

were males (54%) and 440 were females (46%). Average age was 5.2 years. Out of total 959, 562 patients were tested for pandemic influenza (H1N1 2009) and 124 (22%) were confirmed with pandemic influenza (H1N1 2009). This result accounts for 12.7% of total 959 patients. There were no distinctive gender difference between pandemic influenza (H1N1 2009) patients and non-H1N1 patients. Average age for pandemic influenza (H1N1 2009) confirmed patients was 7.5 years old while non-H1N1 patients with 4.6 years old (P<0.001). The contact history with other pandemic influenza (H1N1 2009) patient was found more frequent in the pandemic influenza (H1N1 2009) confirmed cases than non-H1N1 cases (P=0.03). No other symptoms or travel history were different between them.

2. Symptoms

Most common symptoms of confirmed pandemic influenza (H1N1 2009) patients were fever, cough, rhinorrhea, sore throat, sputum; some had headache, myalgia, vomiting, abdominal pain, nausea and diarrhea (Table 1). Similar symptoms were found in non-H1N1 patients. Based on symptoms, it could not be possible to differentiate patients of pandemic influenza (H1N1 2009) from those with other reasons. Only the number of cases with cough was higher in patients with pandemic influenza (H1N1 2009) than other patients (P<0.001). Of total 959 patients, 27 needed hospitalization. Main reasons for hospitalization were pneumonia and dehydration caused by fever.

Table 1. Clinical Features of Patients with Flu-like Illness

	H1N1	Other viruses	*P* value
Sex (%, male)	54	54	0.518
Contact history (%)	80	42	0.000
Travel history (%)	6	20	0.018
Fever (%)	95	94	0.361
Cough (%)	85	71	0.001
Sputum (%)	48	46	0.43
Rhinorrhea (%)	71	71	0.533
Sore throat (%)	73	77	0.358
Nasal obstruction (%)	50	74	0.048
Myalgia (%)	61	43	0.183
Lethargy (%)	24	33	0.305
Headache (%)	43	58	0.169
Nausea (%)	11	6	0.221
Vomiting (%)	18	17	0.46
Diarrhea (%)	10	15	0.269
Abdominal pain (%)	25	50	0.044

H1N1, pandemic influenza (H1N1 2009) virus
The proportions of each symptom were derived from different numbers of patients recognized according to each symptom.

3. Patients needed to be hospitalized

A total of 27 patients needed to be hospitalized. Of them, 10 patients were confirmed as pandemic influenza (H1N1 2009). These 10 patients accounted for 8.1% of total 124 confirmed pandemic influenza (H1N1 2009) patients. Severe productive cough with fever and interstitial opacities on their chest radiographs were manifested, which were consistent with pneumonia. On the contrary, 14 out of 17 non-H1N1 patients were hospitalized due to pneumonia, one of which had a croup. Two of 17 non-H1N1 patients were hospitalized due to dehydration from high fever, one of which was confirmed as urinary tract infection. Remaining 1 patient of 17 non-H1N1 patients was hospitalized given febrile convulsion with high fever. Average age hospitalized patients was 5.5 years in confirmed pandemic influenza (H1N1 2009) patients and 2.6 years in non-H1N1 patients (P=0.008).

Of those patients with confirmed pandemic influenza (H1N1 2009), 2 with pneumonia showed anti-Mycoplasma IgG above a titer of 1:320 and were regarded as Mycoplasma co-infection. Other bacterial pathogens had not been identified. Two cases of pneumonia were caused by adenovirus in non-H1N1 patients. No other reasons for pneumonia were found in the remaining cases.

We also noted that leukocyte value was relatively lower in patients with pandemic influenza (H1N1 2009) than in non-H1N1 pneumonia patients (6,690/mm^3 vs 12,097/mm^3, P=0.080). C-reactive protein increased in patients with pandemic influenza (H1N1 2009) as non-H1N1 patients showed (21 vs 44.9, P=0.065). Erythrocyte sedimentation rate did not increase in pandemic influenza (H1N1 2009) patients (11.5 mm/hour vs 32.9 mm/hour, P=0.033). ALT levels in pandemic influenza (H1N1 2009) patients were in the normal range. Patients with pandemic influenza (H1N1 2009) showed distinct electrolyte imbalance of hyponatremia and hyperkalemia (124 mEq/dL, 5.2 mEq/dL respectively, P=0.015, P=0.021) (Table 2).

Symptoms of 8 patients with confirmed pandemic influenza (H1N1 2009) improved just with oseltamivir at the dose recommended by WHO together with ampicillin-sulbactam or amoxicillin-clavulanate. Within 2 days of hospitalization, other two patients showed dyspnea accompanying wheezing and rapid progressive pneumonia even though they were taking the oseltamivir. One of them showed bilateral patchy alveolar opacities during hospitalization. They needed additional antibiotics of glycopeptides and corticosteroid together with intravenous immunoglobulin. Clinical improvement was achieved after the additional treatments in 5 days without management at intensive care unit. These patients recovered without other complications. Average hospitalization was 4.2 days (3 to 7 days). There were no

Table 2. Laboratory Features of Hospitalized Patients

	H1N1	Other viruses	*P* value
Age (years)	5.5±4.4	2.6±1.8	0.017
White blood cell (/μL)	6690±2755.8	12097.1±7203.9	0.08
Hemoglobin (g/dL)	12.2±0.7	11.5±0.9	0.445
Platelet (/μL)	245777.8±82203.7	274571.4±88277.3	0.576
ESR (mm/hour)	11.5±9.2	32.9±23.5	0.033
CRP (mg/L)	21±22.5	44.9±45	0.065
Ca (mg/dL)	9.3±0.6	9.2±0.4	0.126
Phosphorus (mg/dL)	4.7±0.5	4.2±0.8	0.069
Glucose (mg/dL)	105.3±10.1	96±13.8	0.339
BUN (mg/dL)	8.6±2.2	10.8±5.6	0.177
Creatinine (mg/dL)	0.5±0.1	0.4±0.1	0.276
Uric acid (mg/dL)	4±1.1	4.3±1.4	0.534
Cholesterol (mg/dL)	143.2±10	134.2±26.3	0.001
Protein (g/dL)	6.6±0.5	6.7±0.7	0.207
Albumin (g/dL)	4.5±0.3	4.3±0.3	0.438
AST (IU/L)	62.3±61.6	37.4±15.3	0.001
ALT (IU/L)	34.9±47.6	16.1±7.5	0.006
Na (mmol/L)	124±40.5	137.2±2.5	0.015
K (mmol/L)	5.2±3	4.2±0.3	0.021
Cl (mmol/L)	103.6±1.9	103.3±2	0.826

H1N1, pandemic influenza (H1N1 2009)

patients with neurological or cardiac complications.

4. Other respiratory viruses

During the same period, We investigated 216 additional hospitalized patients with acute respiratory infectious disease for causative viruses by multiplex RT-PCR such as pneumonia, bronchiolitis, croup or acute respiratory distress syndrome. They showed negative result with H1N1 2009 RT-PCR. Causative viruses were found in 151 (69.9%) out of 216 patients. Among them, there were 121 cases with rhinovirus (56%), 31 with adenovirus, 17 with bocavirus, 2 with seasonal influenza, 3 with respiratory syncytial virus, 2 with parainfluenza virus and 1 with coronavirus (Fig. 2).

Discussion

The first case with pandemic influenza (H1N1 2009) in Korea was an adult who traveled in an epidemic country and came back with febrile symptoms (3). We believe that there has been continuous inflow from overseas since then and spread rapidly. In this study, we showed that children with flu-like illness in the early phase of pandemic influenza (H1N1 2009) pandemic had been affected not only by pandemic influenza virus, but also by various seasonal viruses.

While influenza virus used to be the major virus causing

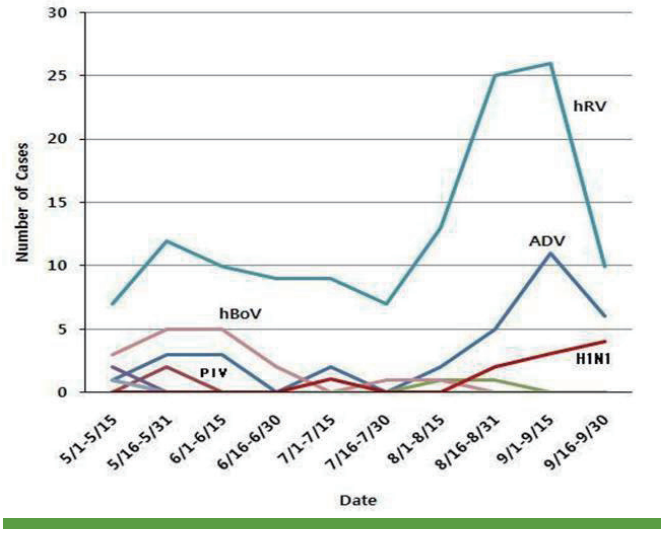

Figure 2. Various respiratory pathogenic viruses circulated during early phase of pandemic. Rhinovirus and adenovirus caused the respiratory infection in children at the same time with pandemic influenza (H1N1 2009) virus.
ADV, adenovirus; PIV, parainfluenza virus; hRV, human rhinovirus; hBoV, human bovca virus; H1N1, pandemic influenza (H1N1 2009)

respiratory diseases in winter, pandemic influenza (H1N1 2009) became a major concern because the virus was new type. When we treated patients, pandemic influenza (H1N1 2009) was becoming important issue in judging clinical treatment. Pandemic influenza (H1N1 2009) which had started to prevail during summer in Korea was a new menace and its speed of spread had been known as faster than any other influenza viruses. In addition, although the case fatality of pandemic influenza (H1N1 2009) was known to be similar to that of seasonal influenza, there had been many reports on deaths related to pandemic influenza (H1N1 2009). Accordingly, in clinical setting, it was important to diagnose whether pandemic influenza (H1N1 2009) infection has occurred or not, and to start empirical treatment for children.

In this report, we performed a diagnostic test for pandemic influenza (H1N1 2009) which accounts for 60.4% of total patients with flu-like illness. Of these, we diagnosed 22% confirmed cases which account for 12.9% of total visited patients. Clinically, there were several distinctive characters in pandemic influenza (H1N1 2009) infected patients. The most distinctive one between H1N1 patients and non-H1N1 patients was age. Age of H1N1 patients average 7.2 years old. Those hospitalized patients due to confirmed H1N1 were aged over 5 years old. It has been known that patients with lower respiratory tract infection due to other respiratory viruses including seasonal influenza are mostly found for children below 3 years old; and RSV are most commonly found in children under 12 months old (9, 10). Considering fast transmission speed of pandemic influenza (H1N1 2009) (11), it

could explain that children in kindergartens or school would show high incidence. Secondarily, most patients had contact history with other patients with H1N1 infection. The patient's history would be important clue for exploring cause of their symptoms.

Also, we need to consider other viruses in managing the patients. Of total flu-like illness, 13% were confirmed pandemic influenza (H1N1 2009). Other viruses including adenovirus, human bocavirus and human rhinovirus were identified in about 70% of the hospitalized patients with respiratory infection. It is difficult to differentiate the causative agents just with symptoms and physical examination of patients. This difficulty of making clinical diagnosis leads inappropriate use of antibiotics or antiviral agents like oseltamivir. Despite the mild presentations of pandemic influenza, the public response to novel viral disease had to make care burden in Korea, particularly in tertiary hospital. Reports of deaths from the pandemic influenza contributed to excessive visit to tertiary hospital where the Korean Center of Disease Control and Prevention assigned for control of pandemic influenza. In a condition of similar level of virulence with seasonal flu and high transmissibility, the antiviral therapy and chemophylaxis were recommended to limited persons who are hospitalized with severe flu-like illness, contact with a known patient and high risk of complications from influenza (12). Our experience suggests that the conservative management of mild flu presentation is recommendable as a measure against re-attack of virus next season.

Thirdly, laboratory characteristics in influenza A (H1N1) infection, revealed less dominant leukocytosis, less inflammatory signs, and rapid progressive electrolytes imbalance. In cases of seasonal influenza, Fas–Fas ligand signaling induces apoptosis, and plays a major role in regulating leukocyte population (13). In children with pandemic influenza (H1N1 2009), electrolytes imbalance, particularly hypokalemia (15, 16) or hyperkalemia (17) was reported of which mechanism are unknown. In our patients with hyperkalemia or hyponatremia, they recovered soon after sufficient hydration. The levels of cholesterol and ALT were significantly higher than those in non-H1N1 patients, but in normal ranges; and the cause of their change is to be studied.

In the treatment for pandemic influenza (H1N1 2009) conservative treatment and antiviral agent like oseltamivir were important. But in severe cases of complicated rapid progressive pneumonia, we tried antibiotics and corticosteroid. The use of antibiotics is well accepted treatment for secondary bacterial pneumonia following the influenza. Even if corticosteroid use for influenza is well supported. The use of corticosteroid seem likely to reduce the inflammatory response in acute phase of influenza or other respiratory virus infection (18). Because the excessive inflammation is known to be the major cause of mortality in influenza pneumonia (19), corticosteroid is thought to be the treatment of choice for some patients with complicated severe pneumonia or respiratory difficulty.

Our study has some limitations. This is a small case series from a tertiary medical center in Seoul, Korea and our findings may not be generalized to other pediatric populations. The number of subjects with pandemic influenza (H1N1 2009) may have been underestimated as some visited patients were excluded from pandemic influenza (H1N1 2009) test because of its expensive costs. Some parents of patients asked for antiviral agent therapy without test.

To our knowledge, this is the first report to show concurrent viral diseases with pandemic influenza (H1N1 2009) in pandemic period and to describe the clinical features in children in Korea. Conclusively, during early phase of pandemic influenza (H1N1 2009) pandemic various respiratory viruses were also important causes for flu-like illness, while some patients were confirmed as pandemic influenza (H1N1 2009) and hospitalized. Age population and contact history were distinct features and could be an important clue to discriminate causes in patients with febrile respiratory symptoms.

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