

Hospitalized Cases of Adolescent and Adult H1N1 Influenza in a University Hospital in Korea, September 2009-January 2010

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H1N1 Influenza 입원 환자의 임상적 특징에 대한 연구 (2009.10-2010.1)

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연구배경 : 2009년 4월 새로운 인플루엔자 A(H1N1) 바이러스에 의한 감염은 전세계적으로 대유행이 시작되었다. 본 연구에서는 대한민국의 한 대학병원에서 발생한 H1N1 인플루엔자 감염환자 중에서 청소년과 성인 입원 환자를 대상으로 임상적 특성과 예후에 대하여 2009년 9월부터 2010년 1월까지 조사하여 알아보고자 하였다.

방 법 : 대유행 H1N1 인플루엔자로 확진된 13세 이상의 환자의 의무기록을 후향적으로 분석하였으며 대유행 H1N1 인플루엔자는 real-time reverse transcriptase-polymerase chain reaction 시행하여 확진하였다.

결 과 : 43명의 대유행 인플루엔자 입원 환자 중에서 7명(16%)은 중환자실 치료를 받았으며 이중 1명(2%)은 사망하였다. 평균 연령은 45세였고 기저질환으로 천식, 당뇨, 허혈성 심장질환, 기관지 확장증, 암의 순서로 많은 빈도수를 보였다. 임상증상으로 발열이 가장 주된 증상이었으며 그 외에 기침, 호흡곤란, 콧물, 근육통 또는 관절통, 인후통을 호소하였다. 입원 시 42명 중 25명의 환자에서 흉부 방사선 검사 결과 폐렴을 동반하였고 만성호흡기 질환의 악화를 보인 경우가 11명의 환자에서 관찰 되었다. 또한 23명의

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환자에서 산소공급이 필요하였으며 이중 2명은 급성 호흡부전으로 인하여 기계 환기가 필요하였다. 중환자실 입원을 요한 7명의 환자들은 모두 기저질환을 가지고 있었으며 이중 5명은 천식, 3명은 허혈성 심장 질환이 있었고 임신 상태와 당뇨가 각각 1명으로 나타났다. 확진된 모든 환자들은 증상 발현으로부터 평균 2일 내에 항바이러스제를 처방 받았다.

결론 : 천식은 입원치료를 요하는 대유행 인플루엔자 감염환자에서 가장 흔하게 동반된 내과적 질환이었으며 특히 허혈성 심장질환 동반하는 환자의 경우 중환자실 입원을 필요로 함을 알 수 있으며 연구 결과 대부분의 환자에서 항바이러스제 치료에 효과적인 것으로 나타났다.

중심 단어 : 대유행 인플루엔자(H1N1) · 천식 · 허혈성 심장질환.

Introduction

In April 2009, a novel influenza A(H1N1) virus that originated in swine caused human infection in Mexico and the United States. Within a few months, the H1N1 influenza pandemic spread worldwide. Concern about H1N1 influenza infection has heightened with the ongoing circulation of the 2009 H1N1 influenza strain. The first case of H1N1 influenza in Korea was diagnosed on 2 May 2009, and this was followed by multiple human-to-human transmissions. Most of these infections occurred in young adults, and few hospitalizations resulted¹⁻³. Patients with risk factors for severe illness from seasonal influenza, such as chronic lung disease, immunosuppression, diabetes, and pregnancy, also appear to be at risk of severe pandemic H1N1 influenza infection⁴. Because these groups have been targeted for 2009 H1N1 vaccination by the Centers for Disease Control and Prevention(CDC), a significant decrease in the number of hospitalizations for 2009 H1N1 was seen in patients with known risk factors.

To date, limited research and structured data are available to assess the risk factors associated with severe cases of this illness requiring hospitalization in Korea or the clinical outcomes of these cases. Therefore, we present our experience with patients admitted to the hospital with pandemic H1N1 influenza. We describe the clinical characteristics and prognosis of adolescents and adults hospitalized with H1N1 influenza in a university hospital in Korea from September 2009 to January 2010.

Methods

We reviewed the charts of all adolescents and adults admitted to the Ewha Medical Center with laboratory-

confirmed pandemic H1N1 influenza. This hospital serves as the referral center for the surrounding region for patients with influenza-like illnesses, including 2009 H1N1 virus infection. A nasopharyngeal swab was obtained for a real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR), and all testing was based on standard CDC-based primers. From 21 August 2009, when the diagnostic rRT-PCR test became available at our hospital, until 31 January 2010, 3,788 cases of H1N1 aged 13 or older were confirmed at Ewha Medical Center, Korea. Over the 5 months of the study, 43(1.1%) patients aged 13 years and older were admitted to our hospital with pandemic H1N1 influenza confirmed using rRT-PCR. We excluded those patients admitted for another illness more than 3 days before the onset of influenza-like symptoms, as the flu-like illness was deemed incidental to their admission.

The patients' demographic characteristics, underlying medical conditions, clinical signs and symptoms, laboratory findings, radiologic features, and treatment course and clinical outcome were obtained from their medical records. At admission, serum chemistry profiles, arterial blood gases, and chest radiographs were examined. We collected data on the occurrence of sepsis, viral meningitis, and pulmonary complications, including pneumonia, pleural effusion, respiratory failure requiring mechanical ventilation, and an exacerbation of underlying chronic lung diseases. The study was approved by the internal review board of our institution, and the requirement for individual patient consent was waived for this retrospective study.

SPSS version 17.0 was used for the statistical analysis. A *p* value <0.05 was deemed to indicate statistical significance. Group comparisons of categorical variables were made using Pearson's chi-square(χ^2) test or Fish-

er's exact test. For comparisons between two groups, we used Student's t-test for normally distributed data or the Mann-Whiney U-test for non-normally distributed data.

Results

1. Clinical features and underlying medical conditions

The demographic and clinical characteristics of the 43 hospitalized patients are summarized in Tables 1 and 2. The median age was 45 years(range 13–82 years), and 30 patients(70%) were female. Six patients(14%) were aged 65 years or older. Our data showed that most of the cases of severe illness occurred during a wave in November and December 2009, and the incidence subsequently decreased. Fever was the most common symptom(42 patients, 95%), and other symptoms in descending order of frequency included cough(84%), shortness of breath (40%), rhinorrhea(30%), myalgia or arthralgia(23%), sore throat(21%), headache(16%), and chest discomfort (5%). Six patients(14%) presented with gastrointestinal symptoms consisting of isolated vomiting in five and vomiting with diarrhea in one.

Twenty-six cases(56%) had underlying medical conditions previously reported as risk factors associated with severe H1N1 influenza^{2,4-6)}. The most common medical conditions in descending order of frequency were asth-

Table 1. Characteristics of 43 adolescent and adult hospitalized patients who were confirmed to be infected with H1N1 influenza(September 2009–January 2010)

| Characteristic | n=43 |
|--|-----------------|
| Age, years | 45(13–82) |
| 13–17 yr | 10(23) |
| 18–49 yr | 15(35) |
| 50–64 yr | 12(28) |
| ≥65 yr | 6(14) |
| Female gender, n(%) | 30(70) |
| Body mass index, kg/m ² (n=40)* | 22.5(15.0–32.0) |
| The time of hospitalization | |
| September 2009 | 1(2) |
| October 2009 | 7(16) |
| November 2009 | 20(47) |
| December 2009 | 12(28) |
| January 2010 | 3(7) |

Values are expressed as the median(range) or number(%). * : The BMI was not calculated in three pregnant women

ma(30%), diabetes(19%), ischemic heart disease(9%), bronchiectasis(7%), malignancy(7%), pregnancy(7%), cerebrovascular disease(5%), chronic obstructive pulmonary disease(2%), and chronic renal disease(2%)(Table 3). Chronic respiratory disease was noted in 17 of the 43 patients(40%). Of the three pregnant patients, one was in the first trimester, and two were in the third trimester. Malignancy included acute myeloblastic leukemia, cervical cancer, and breast cancer with thyroid cancer in one patient each.

2. Diagnostic findings

Table 4 summarizes the laboratory results in the pa-

Table 2. Clinical signs and symptoms in the patients

| Characteristic | n=43 |
|--|-----------------|
| Clinical symptoms | |
| Time from the onset of illness to admission, day | 2(1–10) |
| Fever | 41(95) |
| Duration of fever, days | 1(0–11) |
| Cough | 36(84) |
| Shortness of breath | 17(40) |
| Rhinorrhea | 13(30) |
| Myalgia or arthralgia | 10(23) |
| Sore throat | 9(21) |
| Headache | 7(16) |
| Vomiting | 6(14) |
| Chest discomfort | 2(5) |
| Diarrhea | 1(2) |
| Clinical signs on admission | |
| Temperature, °C | 37.9(36.4–39.4) |
| Respiration rate, /min | 20(18–34) |
| Systolic blood pressure, mmHg | 120(85–180) |
| Diastolic blood pressure, mmHg | 70(50–110) |

Values are expressed as the median(range) or number(%)

Table 3. Underlying medical conditions of the patients

| Characteristic | n=43 |
|---------------------------------------|--------|
| Chronic respiratory disease | |
| Asthma | 13(30) |
| Bronchiectasis | 3(7) |
| Chronic obstructive pulmonary disease | 1(2) |
| Diabetes mellitus | 8(19) |
| Ischemic heart diseases | 4(9) |
| Malignancy | 3(7) |
| Pregnancy | 3(7) |
| Cerebrovascular disease | 2(5) |
| Chronic renal disease | 1(2) |

Values are expressed as the number(%)

Table 4. Laboratory findings in the patients

| Characteristic | n=43 |
|---|--------------------|
| Hemoglobin, g/dL | 12.9(7.9 – 16.9) |
| White-cell count, per mm ³ | 8500(2400 – 22900) |
| Neutrophils, % | 77.3(25.6 – 94.9) |
| Lymphocytes, % | 13.4(1.0 – 65.2) |
| Monocytes, % | 7.2(0.9 – 16.6) |
| Platelet count, × 10 ³ per mm ³ | 205(82 – 331) |
| Arterial blood gas analysis(room air) (n=32) | |
| PaO ₂ (mmHg) | 70.8(42.1 – 114.8) |
| PaCO ₂ (mmHg) | 33.5(25.1 – 42.4) |
| Biochemistry | |
| Albumin, g/dL | 3.7(2.1 – 5.0) |
| BUN, mg/dL | 12(4 – 43) |
| Creatinine, mg/dL | 0.9(0.5 – 2.1) |
| Alanine aminotransferase, U/L | 24(9 – 137) |
| Aspartate aminotransferase, U/L | 16(5 – 145) |

Values are expressed as the median(range) or number (%)

tients. Fifteen of the 43 patients tested(35%) had leukocytosis, seven(16%) had leucopenia, and six(14%) had thrombocytopenia on admission⁷. Fifteen of the 32 patients tested had hypoxia with a resting PaO₂ <70 mmHg. Bacterial infections that were identified from sputum cultures included methicillin-resistant *Staphylococcus aureus* in a 49-year-old man with necrotizing pneumonia and parapneumonic effusion and *Klebsiella pneumoniae* in a 79-year-old bedridden woman who had pneumonia and underlying cerebrovascular disease. Two of 41 patients had positive blood cultures : a 54-year-old woman with pneumonia who had a positive urinary antigen test and blood cultures positive for *Streptococcus pneumoniae* and a 68-year-old woman with acute respiratory distress syndrome who had blood cultures that were positive for *Enterococcus faecium*. Three of 36 patients had positive tests for *Mycoplasma* IgM and two of the three had radiographic changes compatible with pneumonia.

Chest radiograph findings were available for 42 of 43 patients ; the pregnant woman in the first trimester was excluded. Twenty-five of 42(60%) had radiologic findings compatible with pneumonia, and 17 of these patients (68%) had bilateral infiltrates. Lesions were regarded as central in 12(48%), peripheral in four(16%), central mixed with peripheral in six(24%), and diffuse in three(12%). Common patterns of parenchymal abnormalities in order

Table 5. Medical treatment in the patients

| Characteristic | n=43 |
|--|-----------|
| Antiviral therapy | |
| Oseltamivir | 41(95) |
| Zanamivir | 2(5) |
| Days from onset of illness to initiation of treatment | 2(1 – 10) |
| Before admission | 15(35) |
| On admission | 22(51) |
| More than 48 hrs after admission | 6(14) |
| Antibiotic treatment | 43(100) |
| Corticosteroid treatment | 14(33) |
| Oxygen supplement | 23(54) |

Values are expressed as the median(range) or number (%)

of frequency included ground-glass opacity(GGO) in 18(72%), consolidation in five(20%), and a mixed pattern of GGO and consolidation in two(8%). Pneumomediastinum was seen in three and pleural effusions in two.

3. Medical treatment

All patients were given antiviral therapy with oseltamivir, which was initiated a median of 2 days(range 1 – 14 days) after the onset of illness(Table 5). However, two patients developed severe diarrhea after taking oseltamivir, and they were treated with zanamivir. Antiviral therapy was started before admission in 15 patients(35%), on admission or within 48 hours after admission in 22 patients (51%), and more than 48 hours after admission in six patients(14%). All received parenteral antibiotics, and 51% patients received more than one antibiotic. Commonly used antibiotics included β-lactam with macrolide in 17 patients, β-lactam only in ten, respiratory fluoroquinolone in nine, anti-pseudomonal β-lactam only in two, anti-pseudomonal β-lactam with macrolide in two, anti-pseudomonal β-lactam with fluoroquinolone in two, and anti-pseudomonal β-lactam with clindamycin in one. In addition to these antibiotics, anti-methicillin-resistant staphylococcal glycopeptides were used in three patients.

Fourteen patients(33%) received corticosteroids ; of these patients, ten had asthma, and one had chronic obstructive pulmonary disease. One patient with acute myeloblastic leukemia had presumed pneumonia with a pattern of bronchiolitis obliterans organizing pneumonia radiologically, and a pregnant woman in the third trimester had viral pneumonia and bronchospasm(with no his-

Table 6. Clinical outcomes in the patients

| Characteristic | n=43 |
|--|------------|
| Pulmonary complications | |
| Pneumonia | 25(58) |
| Exacerbation episode of chronic respiratory disease | 11(26) |
| Pneumomediastinum | 3(7) |
| Parapneumonic effusion | 2(5) |
| Sepsis | 2(5) |
| Viral meningitis | 1(2) |
| ICU admission | 7(16) |
| Acute respiratory failure requiring mechanical ventilation | 2(5) |
| Duration of hospitalization, days | 5 (1 – 28) |

Values are expressed as the mean \pm SD, median(range) or number(%).

tory of asthma).

4. Clinical outcomes

The overall clinical outcomes are summarized in Table 6. Twenty-five patients had radiologic findings at admission consistent with pneumonia, and 11 had an exacerbation of chronic respiratory disease. Twenty-three needed supplemental oxygen due to hypoxia; of these, two developed acute respiratory failure requiring mechanical ventilation. Two had clinical diagnoses of sepsis, and one had viral meningitis. Two had parapneumonic effusions confirmed by diagnostic thoracentesis.

Of the 43 patients hospitalized, seven(16%) were admitted to the intensive care unit(ICU), and one(2%) died. The median duration of hospitalization was 5 days(range 1–28 days). All seven patients admitted to the ICU had underlying conditions, including asthma in five, ischemic heart disease in three, and pregnancy and diabetes in one each. Among these, six were diagnosed with severe pneumonia, two with heart failure, one with shock, and one with acute renal failure requiring continuous renal replacement therapy(CRRT). One pregnant woman(40 weeks gestation) who had preeclampsia and viral pneumonia required ICU care after delivery. In a 68-year-old woman with radiologic evidence of pneumonia and multiple medical problems, including hypertension, asthma, and diabetic nephropathy, blood cultures yielded *E. faecium*. Five days passed between the onset of her illness and the initiation of antiviral therapy; oseltamivir was started 4 days after admission. She had acute respiratory

distress syndrome, newly developed ischemic heart disease, and acute renal failure requiring CRRT, and died eight days after admission.

Comparison of the patients who were and were not admitted to the ICU showed no significant differences in age($p=0.742$), gender($p=0.655$), body mass index($p=0.101$), time from the onset of illness to admission or initiation of antiviral therapy($p=0.393$), and history of diabetes($p=1.000$), pregnancy($p=0.421$), or radiographically confirmed pneumonia($p=0.209$). Patients who were admitted to the ICU had higher respiratory rates($p=0.032$) and lower PaO₂ levels($p=0.007$) on admission than did patients who were not admitted to the ICU. All but one of the patients with ischemic heart disease($p=0.010$) and 38% of the patients with asthma($p=0.172$) required ICU care.

Discussion

Since a novel pandemic influenza A(H1N1 2009) was first reported in Mexico in April 2009, this 21st century pandemic influenza had been spreading from the North America to all over the world. In Korea, May 2, 2009 51 year old female patient who visited Mexico was first diagnosed as H1N1 influenza and overseas tourists and foreigners entering the peninsula were diagnosed and isolated. Nevertheless, the outbreak of the community started, and the number of patients increased exponentially. The most notable feature of this pandemic influenza(H1N1 2009) were that the hospitalization rate and mortality rate of young age group was especially high. Compared with seasonal influenza, the symptoms of respiratory system were similar, on the contrary, gastrointestinal symptoms, such as diarrhea and vomiting, were combined up to 20–35%. According to the other countries reports, patients with body mass index(BMI) 30 or more is the definite high risk group.

During this catastrophic event, the Ewha womans University of Mokdong Hospital was assigned as a regional center of Western part of Seoul. To understand the epidemiology, clinical characteristics and risk factor, we investigated the PCR-confirmed patients with history of admission. In our series of a small number of cases hospitalized with pandemic H1N1 influenza infection at a university hospi-

tal in Korea, 23% were adolescents younger than 18 years, 63% were between the ages of 18 and 49 years, and 14% were 65 years of age or older. Less than one third of the patients who were admitted to the ICU were over 65 years of age. The presenting clinical features of pandemic H1N1 influenza in our series were similar to those described recently for pandemic 2009 H1N1 in other countries^{1-4,8,9)} and during the peak periods of seasonal influenza¹⁰⁻¹²⁾. It predominantly affects young adults, with relative sparing of older age groups. The natural course of H1N1 influenza infection appears to be mild, and most patients recover^{14,9)}. In our series, most patients seemed to benefit from antiviral therapy, although a 68-year-old woman with pneumonia and multiple medical problems died. She newly developed ischemic heart disease during her admission, and this was followed by multiple organ failure, including acute renal failure and acute respiratory distress syndrome. More than half of the patients developed pneumonia with or without secondary bacterial infections ; fortunately, most of the patients hospitalized with pneumonia recovered rapidly.

In our series, the time from symptom onset to the initiation of antiviral therapy was shorter than seen in the United States⁴⁾, and this may be due to the stage of the pandemic. Although the first case of pandemic H1N1 influenza in Korea was diagnosed in May 2009, our hospital acquired a confirmative diagnostic tool for H1N1 influenza infection on 21 August 2009. Therefore, progression of the pandemic may have reduced the threshold for early visits to hospital and enabled clinicians to become more experienced in treating pandemic H1N1 infection. In addition, surveillance data from the Korea Centers for Disease Control and Prevention(KCDC) were very important for understanding the pandemic in Korea. Moreover, our study subjects were adolescents or older, and no infants or children were included ; this may be reflected in the lower rate of hospitalization in our study compared to other countries³⁾.

Risk communication and hospital preparedness are key factors for reducing mortality from H1N1 infection. Our results demonstrated that the outbreak caused severe illness requiring hospitalization in the ICU, especially in patients with ischemic heart disease and asthma. Particularly, a related factor requiring ICU admission was isch-

emic heart disease. Based on the data from previous studies^{13,14)}, as the mortality from pandemic H1N1 influenza infection increases, so does the mortality from observed coronary heart disease. The reduction in death rates from coronary heart disease could be partially attributed to the continuing decline in influenza activity and the absence of extensive influenza epidemics. In addition to reinfection-driven autoimmune reactivation of endothelial inflammation leading to acute coronary heart disease events or chronic progression of vascular disease, another probable mechanism is that flu infection or the immune response to it interferes with lipid metabolism, leading to increased susceptibility to high serum cholesterol levels. However, only four patients in our series had ischemic heart disease ; therefore, our results should be complemented by further observational studies to assess the risk factors for H1N1 infection in Korea. Asthma was the most common underlying medical condition in our subjects, although it was not significantly associated with ICU admission. As in patients with seasonal influenza¹⁵⁻¹⁷⁾, asthma is associated with an increase in the incidence and severity of 2009 H1N1 influenza in both children and adults compared to patients without asthma regardless of its severity^{4,9,18)}. In addition, children with pandemic H1N1 influenza were more likely to have asthma than children with seasonal influenza¹⁸⁾. The contractility of airway smooth muscle plays an important role in the pathophysiology of several bronchial disorders. Increased contraction of airway smooth muscle during asthma and respiratory H1N1 infection has been attributed to the release of various broncho-active mediators. A previous study reported that H1N1 infection induced bronchoconstriction, and the most prominent response was observed 48 to 72 hours after H1N1 influenza infection¹⁹⁾.

The H1N1 influenza outbreak caused severe illness requiring hospitalization in patients with asthma, diabetes, cardiovascular disease, and malignancy, and in pregnant women in this study. Previously known ischemic heart disease was associated with the need for ICU care ; however, as our series included few ICU patients, it is difficult to draw firm conclusions. Further observations are needed to substantiate our tentative findings. With early antiviral therapy and the program of protective vaccina-

tion for H1N1 influenza instituted by the KCDC, the number of H1N1-infected and hospitalized patients has decreased. However, enhanced surveillance of ICU cases should be continued in Korea, which may provide more information on severe complications in these patients to plan prevention strategies and management.

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