Clinical Study of the Time Course of Clinical Symptoms of Pandemic (H1N1) 2009 Influenza Observed in Young Adults during an Initial Epidemic in Kobe, Japan

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Abstract

Objective Although the rates of reported symptoms of Pandemic (H1N1) 2009 influenza virus infection are well studied, the course of progression of these symptoms is not clear. In this study, we carefully reviewed the progress of each patient after hospitalization and clarified the clinical course of the symptoms.

Methods We retrospectively examined the clinical data of 16 consecutive patients who had been hospitalized during the early stages of an influenza epidemic and observed the clinical progression of their symptoms.

Results Each symptom had a different time of onset and progression pattern. In roughly one-third of our patients, symptoms appeared before the onset of high fever. Acute respiratory symptoms tended to last longer than other symptoms; similarly, sore throat and cough lasted longer than rhinorrhea. The SpO2 of the patients with influenza showed a declining trend. The point at which minimum SpO2 levels were noted was approximately 1.5 days after onset of fever.

Conclusion In this H1N1 epidemic, patients typically tended to experience general fatigue, sore throat, and cough before the onset of fever, with sore throat and cough lasting longer than the other symptoms. Most patients showed decreased SpO2 levels at 1.5 days after onset of fever.

Key words: Pandemic (H1N1) 2009 influenza, clinical symptoms, time course, young adults, Japan

this information, it is not possible to conclude which complications will be experienced by a particular patient. Further, it is not known whether fever is the first symptom. It is important to understand these aspects due to the widespread prevalence of this infection. Therefore, in this study, we aimed to describe the disease course, including symptom progression. We expect this information to be very useful in the diagnosis and treatment of this infection.

In Japan, the first case of H1N1 infection was that of a traveler from Canada, reported on May 8, 2009. A week later, on May 16, 3 high school students from Kobe City in Japan were confirmed to have Pandemic (H1N1) 2009 influenza virus infection. These 3 cases were not epidemiologically linked to any previously reported cases of individuals who had traveled abroad. Additional cases were subsequently identified from the northern and western parts of Hyogo Prefecture as well as from the neighboring Osaka Prefecture (7, 8). Under the Japanese Infectious Diseases Control Law, patients with clinical indications of disease must initially be hospitalized for 3 days. However, the number of patients was increasing very rapidly: as of May 19, 2009, a total of 163 laboratory-confirmed cases had been reported nationally. Hence, every patient could not be hospitalized. Therefore, from May 18, 2009 onward, only those who needed hospitalization on the basis of clinical indications were hospitalized in Kobe City (in Hyogo Prefecture) and Osaka Prefecture (9).

Accordingly, on May 18, 2009, we hospitalized at our medical center 18 patients who had the less severe clinical indications for admission. We recorded the patients’ clinical symptoms in detail. Further, we treated 16 patients with neuraminidase inhibitors and carefully observed them to determine the timeline of events and the point at which the clinical symptoms disappeared after treatment. In this paper, we report the time course of the observed clinical features.

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<th>Table 1. Characteristics of the 16 Patients with Pandemic (H1N1) 2009 Influenza Virus Infection on Our Hospital Admission</th>
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Patients and Methods

This study was approved by the Regional Ethics Committee of Nishi-Kobe Medical Center, and informed consent was obtained from all the patients. Under the Japanese Infectious Diseases Control Law, patients with influenza-like symptoms and/or influenza confirmed using a real-time polymerase chain reaction (PCR) assay must be hospitalized. Accordingly, 18 patients with Pandemic (H1N1) 2009 influenza were hospitalized at Nishi-Kobe Medical Center during May 16-18, 2009. Two patients were excluded from the treatment regimen: 1 had already been administered oseltamivir and the other was recovering from the infection.

We treated the remaining 16 patients with oseltamivir (75 mg, twice daily) for 5 days. Two patients developed a rash 1 day after the start of oseltamivir treatment, and therefore, we replaced oseltamivir with zanamivir.

The age of the patients ranged from 15 to 33 y (mean, 17.2 y) (Table 1). Of the 16 patients, 15 were high school students aged 15-17 y. The patients were from 4 different high schools of Kobe City. Nine patients (56%) were male. None of the patients had been abroad in the past 1 month, and none of them had diabetes, renal failure, immunosuppressive conditions, chronic lung disease, or cardiac disease. None of the female patients were pregnant. Five patients had underlying conditions: bronchial asthma (2 patients), atopic rhinitis (2 patients), and atopic dermatitis (1 patient). None of the patients were taking medications for any underlying diseases.

Clinical data were recorded prospectively and consecutively with a standard instrument; this data included demographic characteristics, medical morbidities, fever, other symptoms (rhinorrhea, sore throat, cough, general fatigue, headache, myalgia/arthritis, and diarrhea), influenza-related complications, percutaneous oxygen saturation (SpO₂), and clinical outcomes. Of these, the temperature, SpO₂, and clinical symptoms were recorded every 8 hours daily. Subsequently, we reviewed and summarized these data.

Discharge was considered when a patient’s temperature decreased to 37°C for more than 48 hours and/or a patient were for more than 7 days (considered to be the infectious period) and his/her symptoms decreased. The onset of influenza was defined as the time when a patient had high fever (≥38°C) along with at least 1 acute respiratory symptom (rhinorrhea, sore throat, or cough) and Pandemic (H1N1) 2009 influenza virus infection, as confirmed by real-time PCR.

Statistically significant differences in the continuous data were determined using the Wilcoxon rank-sum test (Statview 4.1; ABACUS Concepts, Berkeley, CA). Statistical significance was set at p<0.05.

Results

The duration of patient hospitalization ranged from 3 to 8
days (mean, 4.6 days; Table 1). One patient was hospitalized for 8 days because of low-grade fever and temperature above 37°C. This patient continued to have atopic rhinitis and fever higher than 39°C after hospitalization. None of the patients required intensive care or mechanical ventilation or experienced any complications.

The maximum body temperature ranged from 38.0°C to 39.9°C (mean, 38.8°C) (Table 2); 6 patients (37%) had a body temperature of about 39°C. The time between the onset of influenza and initiation of oral medication was 2-48 hours (mean, 18.2 hours). This large range can be attributed to patients who showed no changes in their SpO2 levels.

The characteristics of our patients closely resemble those reported by studies conducted in America (3, 4, 6, 10). The duration between the onset of fever and the point at which minimum SpO2 levels were noted ranged from 5 to 76 hours (mean, 33.4 hours).

The list of symptoms and the proportion of patients experiencing these specific symptoms is given in Table 3. All patients had fever and cough. Among the 16 patients, 14 (88%) presented with general fatigue and 13 (81%) with rhinorrhea, sore throat, and headache. Eleven (69%) had fever and all upper respiratory tract symptoms, including rhinorrhea, sore throat, and cough.

The time course of each symptom is shown in Fig. 2; the day on which the body temperature started increasing was designated as day 0. Six (38%) patients had cough; 5 (31%), rhinorrhea; 4 (25%), general fatigue; and 3 (19%), sore throat before the onset of fever. Among the 16 patients with cough, 10 (63%) presented with this symptom after the resolution of fever. Among the 13 patients with sore throat, 9 (69%) presented with this symptom after the resolution of fever. Moreover, two days before the onset of fever, 2 (13%) patients had cough; 2 (13%), sore throat; 1 (6%), rhinorrhea; and 1 (6%), general fatigue. The patients’ rhinorrhea resolved simultaneously with the resolution of fever, whereas general fatigue subsided before the resolution of fever. Both headache (observed in 13 patients) and myalgia/arthritis (observed in 7 patients) occurred 1 day after the onset of fever in most cases. Headache and myalgia/arthritis improved rapidly with the resolution of fever.

Discussion

Currently available data indicate that Pandemic (H1N1) 2009 influenza infection is characterized by the symptoms of fever, rhinorrhea, sore throat, cough, general fatigue, headache, myalgia, arthralgia, and diarrhea, of which the most common symptoms are fever and cough (3, 4, 6, 10).

The characteristics of our patients closely resemble those reported by studies conducted in America (3, 10, 11) and Osaka (6) during the early phase of the pandemic. In these reports, the absolute rates of the reported symptoms are similar. However, previous reports did not show the onset and duration of symptoms—information that is essential for operability.
treating a patient. Further, from an epidemiological and clinical perspective, the time course of clinical symptoms is essential; therefore, we report the time course of clinical symptoms in this study.

The number of symptoms experienced by each patient was almost the same but the time course of each symptom was different (Fig. 2). Correspondingly, the area under the curve (AUC) of each symptom was found to be different. The frequency of rhinorrhea, sore throat, general fatigue, and headache was almost the same and more than 80%, whereas the AUC of rhinorrhea and sore throat was greater than that of general fatigue and headache. Therefore, the duration of rhinorrhea and, particularly, sore throat was longer than that of general fatigue and headache. The symptoms preceding the increase in body temperature over 38.0°C were general fatigue and symptoms resembling acute upper respiratory inflammation such as rhinorrhea, sore throat, and cough, typically starting 1-2 days before the onset of high fever; on the other hand, the symptoms following high fever were headache and myalgia. Acute respiratory symptoms tended to last longer than general fatigue, headache, and myalgia, which resolved simultaneously with fever.

We consider that studying the disease progression, that is, the typical onset and course of the illness, is very important. Typical uncomplicated influenza often begins with an abrupt onset of feverishness, chilliness or frank shaking chills, headaches, myalgia, malaise, and anorexia (12). Among the general public, the common belief is that fever is the first sign of infection and they should isolate with this symptom. However, this was not the onset pattern in roughly one-third of our patients. Most patients with the above symptoms would not normally be treated in a hospital; therefore, obtaining clinical information alone is not sufficient. Knowledge of the onset pattern and the typical clinical course would enable clinicians and the general public to better manage Pandemic (H1N1) 2009 influenza infection.

In this study, the duration of sore throat and cough was longer than that of rhinorrhea. The minimum SpO2 level was significantly lower than that at discharge (P = 0.002; Fig. 1). Furthermore, among our 16 patients, 3 (19%) showed a 4% reduction in SpO2 levels. Among these 3 patients, 2 patients had high fever (temperature, 39.1°C and 38.6°C); however, the high fever and minimum SpO2 did not occur simultaneously. This phenomenon can be directly attributed to Pandemic (H1N1) 2009 influenza infection, since most patients had no history of respiratory tract disease and because the lowered SpO2 levels improved with antiviral treatment. It is possible that V/Q mismatch due to lower respiratory tract infection may play a role in the development of this phenomenon. Munster et al. (13) described the pathogenesis of Pandemic (H1N1) 2009 influenza virus in ferret models. They indicated that Pandemic (H1N1) 2009 influenza virus replicated efficiently in the upper and lower respiratory tract of ferrets, and the virus titer was generally higher in throat swabs than nose swabs. Itoh et al. (14) indicated the ability of this virus to replicate efficiently and cause severe pathologic lesions in the lungs of infected mice, ferrets, and nonhuman primates. These results may explain why the duration of cough is longer than that of rhinorrhea, and the patients showed a reduction in SpO2 level after the onset of fever. These phenomena are different from seasonal influenza, and may comprise the characteristics of Pandemic (H1N1)
2009 influenza.

During the 2 weeks after the hospitalization of our 16 patients, approximately 500 febrile patient and/or patients with influenza-like symptoms visited our emergency department. Because of the panic created by the influenza epidemic in Kobe, it was difficult to take chest radiographs of all the patients; we actually did not take it to most patients. However, some of the patients showed a reduction in SpO2 levels. In this study, one of these 3 patients with a 4% reduction had atopic rhinitis. In Japan, a survey revealed that 62.8% of all patients hospitalized between July 28, 2009 and March 23, 2010 did not have any underlying disease (15). Even in the absence of underlying diseases, some patients require hospitalization. Our study reveals that chest radiographs should have been taken at least for patients with lower SpO2 levels. However, we could not develop any standards since this was beyond the scope of this study. However, it must be noted that patients with severe symptoms must not be overlooked in any circumstance.

We treated the patients included in this analysis during the early stage of the H1N1 outbreak; at that time, all the patients visited hospitals for preventing infection. It is important to note that every patient was hospitalized for isolation, and therefore, many patients had no underlying diseases or risk factors. None of the cases were severe or fatal. Most Japanese people do not carry influenza antibodies (14), and there was no vaccine for Pandemic (H1N1) 2009 influenza in Japan at that time of the epidemic. Most patients were infected with this influenza for the first time. Therefore, the outbreak in Kobe showed the natural and typical course for Pandemic (H1N1) 2009 influenza infection.

Our study limitations include a small sample size and a unique study population. Therefore, our data cannot be universally applied. Further, we could not assess the time course of diarrhea, because only a few patients experienced this symptom. Further, the symptoms before hospitalization may have been underestimated since they depend on subjective evaluation by patients.

Conclusion

In conclusion, we report the time course of clinical symptoms of Pandemic (H1N1) 2009 influenza virus infection. From an epidemiological perspective, study of the course of symptoms can help increase public awareness. Further, understanding the clinical course of a typical Pandemic (H1N1) 2009 influenza infection would help clinicians identify influenza infection with or without other complications at an early stage itself. We found that typically, patients experience general fatigue and upper respiratory tract symptoms such as cough and sore throat before the onset of fever. Headache and myalgia appear at the same time as fever and, along with general fatigue, resolve simultaneously with the fever. Cough and sore throat last longer than other symptoms but generally resolve approximately 4 days after the onset of fever. The patients showed a reduction in SpO2 levels at ~1.5 days after the onset of fever.

The authors state that they have no Conflict of Interest (COI).

References


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