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Analysis of Clinical Features of Pandemic 2009 Influenza A (H1N1) Infection using Self-reported Clinical Records of Outpatients

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Clinical features of the pandemic 2009 H1N1 virus infection have been reported mainly in hospitalized patients. We conducted a study using self-reported clinical records of outpatients to analyze their clinical features from November 1, 2009 to February 28, 2010 at Kimura Children and Family Clinic in Izumo, Shimane. A total of 157 records was completed and analyzed. Antiviral treatment with neuraminidase inhibitors was administered to 146 patients (93%). The durations of fever exceeding 37.5℃ and 38.0℃ were 1.5 and 1.1 days, respectively. Fever duration was shorter in patients above 13 years of age ($p<0.05$). Cough was a prominent feature of the infection. Delirious behaviors were observed in 15% of the patients, similar to those observed for seasonal influenza. Our findings suggest that 2009 H1N1 virus infection was mild in outpatients. The mild clinical course may permit individualized treatment, not with uniform use of antiviral drugs.

Key words: pandemic 2009 H1N1 virus infection, clinical features, delirious behaviors, outpatients, antiviral treatment

INTRODUCTION

The 2009 pandemic influenza A (H1N1) epidemic emerged in Mexico and the United States in April 2009, which rapidly spread to other regions of the world [1, 2]. The first cases in Japan were confirmed on May 16, 2009 [3]. The first cases were three students, who were neither sporadically located nor had imported the disease from other countries. The pandemic struck our region; i.e., Izumo, located in western Japan, in August 2009. The number of affected patients peaked in November 2009 and gradually decreased towards the end of February 2010.

Clinical features of 2009 H1N1 virus infection were reported by several studies conducted in the early phase of the pandemic. These studies mainly included hospitalized patients, as summarized by Writing Committee of WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza [4]. A majority of the infected patients demonstrated a mild clinical course. We therefore conducted a study using self-reported records of outpatients to analyze their clinical features. These comprised daily recorded symptoms of infection and body temperature.

METHODS

We conducted a study from November 1, 2009 to February 28, 2010 at Kimura Children and Family Clinic located in Izumo, Shimane. This study was in full conformance with the principles of the Declaration of Helsinki (1964). During this study period, no seasonal influenza A epidemic was reported in Shimane Prefecture including Izumo. Therefore, a positive rapid influenza antigen assays for influenza A was used to diagnose 2009 H1N1 virus infection. Infection was diagnosed if the patient had a positive rapid influenza antigen assays (Immuno-card EX, TFB, INC. Tokyo) or if there was evidence of close contact with patients already diagnosed as influenza A, i.e., 2009 H1N1 virus infection. We also reviewed the total number of patients as well as the number of cases who were referred for hospitalization from our clinic.

The patients or their families were instructed to record their body temperature and symptoms of cough, nasal discharge, sore throat, myalgia and arthralgia, diarrhea, vomiting, loss of appetite, daily

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activity, and delirious behavior on an A4 sized sheet every day until 2 days after fever subsidence. Body temperature was measured and recorded at least twice a day on a graph provided on the sheet. Severity of the symptoms of cough, nasal discharge, sore throat, myalgia, and arthralgia was scored on a scale 0-2 (0 absent, 1 mild, 2 severe). Sore throat, myalgia, and arthralgia were evaluated only for patients ≥ 6 years of age. The instances of diarrhea and vomiting were recorded daily. Appetite was graded on a scale of liquid only, 20%, 50%, 80% and more of the usual intake. Daily activity was graded as ambulatory, sitting, and staying in bed. Delirious behavior was also recorded every day. Each behavior was classified with some modification of the classification given by Yokota et al [5]. These included hallucinatory confusion, delirious utterances, automated behavior, fear, laughing and crying. The duration of fever exceeding 37.5℃ or 38.0℃ was estimated on the body temperature graph. Fever duration, daily activity and appetite were compared among three age groups by using Kruskal-Wallis test. Patients with antiviral treatment started within 24 hours and those over 24 hours were compared among the same age group by using Mann-Whitney's u-test. A P value of less than 0.05 was considered statistically significant. All analyses were performed using JMP 5.0.1a (SAS Institute Inc).

RESULTS

A total of 397 patients with 2009 H1N1 virus infection was seen at Kimura Children and Family Clinic during the study period. Two patients were admitted to nearby hospitals due to respiratory failure immediately after the first visit. From the remaining, 157 self-reported clinical records were obtained, the details of which are listed in Table 1.

Table 1. Clinical characteristics of the 157 patients

Characteristics		n. /total no.(%)
Age	<7yr	59/157 (38%)
	7-13yr	71/157 (45%)
	14-19yr	16/157 (10%)
	20-59yr	10/157 (6%)
	>60yr	1/157 (0.6%)
Symptom	fever	
	peak temperature	
	37.5-38.0℃	7/157(4%)
	38.1-39.0℃	65/157(41%)
	>39.0℃	85/157(54%)
	duration (days (SD))	
	>37.5℃	1.5 (0.6)
	>38℃	1.1 (0.6)
	cough	151/157 (96%)
	sore throat (>5 yr)	66/110 (60%)
	myalgia, arthralgia (>5 y	41/110 (37%)
	diarrhea	49/157 (31%)
	vomitting	29/157 (18%)
	delirious behavior	22/157 (14%)
Antivirals	oseltamivir	129/157(82%)
	zanamivir	17/157 (11%)

The patients were aged between 6 months and 60 years, with a mean age of 10.3 ± 9.5 (standard deviation [SD]) years, and 130 patients (82%) were below the age of 14. All the 157 patients recovered without serious complications during the course of infection.

The mean durations of fever exceeding 37.5℃ and 38.0℃ in this study were 1.5 ± 0.6(SD)days and 1.1 ± 0.6 days, respectively. Fever durations among the age groups of less than 7 years, between 7 and 13 years of age, and above 13 years of age are shown in Table 2. Fever duration was shorter in patients above 13 years of age when compared to those below 7 and those between 7 and 13 years of age; this difference was statistically significant. The duration of poor appetite of 20% or less and staying

Table 2. Fever duration in the three age groups

		fever duration, mean (SD), days			
Age	n (n, % of antiviral therapy)	>38.0℃	*p value	>37.5℃	*p value
<7yr	59 (51, 86%)	1.3 (0.5)		1.5 (0.6)	
7-13yr	71 (70, 98%)	1.2 (0.6)	0.005	1.6 (0.6)	0.046
>13yr	27 (24, 89%)	0.7 (0.6)		1.2 (0.7)	

*Determined by Kruskal-Wallis test

in bed was approximately 1 day (Table 3). Patients between 7 and 13 years of age had longer durations of staying in bed. Cough was recorded in 96% patients. On the first recorded day, 131 patients (83%) already had cough, which was severe in 51 patients. Diarrhea and vomiting were observed in 38% and 18% of patients, respectively.

Delirious behavior was observed in 22 patients (14%) aged between 1 and 12 years, with a mean age of 6.4 ± 2.6 (SD) years. The following was recorded for delirious behavior: 7 patients showed delirious utterances, 6 showed hallucinatory confusion, 4 showed fear, 3 showed crying, 1 showed laughing, and 1 showed automated behavior (Table 4). However, these symptoms were all transient.

Antiviral treatment consisting of neuraminidase inhibitors was administered to 146 patients (93%) (Table 1). There was no difference in fever duration between patients receiving antiviral treatment and those not receiving treatment (Table 5). Fever duration was shorter (0.3-0.7 days) in patients who were given medication within 24 hours, but was statistically significant only in cases belonging to the 7-13 year age group where the duration of fever exceeded 37.5℃ (Table 6).

Table 3. Daily activity and appetite

1) Daily activity

		Duration staying in bed (days)					
Age	n	0	1	2	3	mean	*p value
<7yr	59	28 (47%)	22 (37%)	7 (12%)	2 (3%)	0.7	
7-13yr	71	15 (21%)	31 (44%)	21 (30%)	4 (6%)	1.2	0.003
>13yr	27	12 (44%)	7 (26%)	8 (30%)	0	0.9	

2) Appetite

		Duration of the appetite loss less than 20% as usual (days)						
Age	n	0	1	2	3	4	mean	*p value
<7yr	59	26 (44%)	16 (27%)	13 (22%)	2 (3%)	2 (3%)	1	
7-13yr	71	24 (34%)	27 (38%)	16 (23%)	3 (4%)	1 (1%)	1	0.617
>13yr	27	13 (48%)	7 (26%)	5 (19%)	2 (7%)		0.6	

*Determined by Kruskal-Wallis test

DISCUSSION

The abovementioned results suggested a mild clinical course of 2009 H1N1 virus infection in outpatients. The mean durations of fever exceeding 37.5℃ and 38.0℃ were 1.5 days and 1.1 days,

Table 4. Delirious behaviors

Delirious behaviors	n	Examples
Delirious utterances	7	Meaningless or inappropriate words such as "Merry Christmas
Hallucinatory confusion	6	"The ceiling is swaying.", "My sister became much taller." "I wonder where I am.", "Everything I see is distorted."
Fear	4	It is often associated with crying. "I am scared of the pictures.
Crying	3	
Laughing	1	
Automated behavior	1	Going out to the balcony to change the clothes

Table 5. Antiviral therapy

			fever duration, mean (SD), days	
	n. /total no.(%)	age(SD):years	>38.0℃	>37.5℃
none	11/157 (7%)	8.4 (5.4)	1.2 (0.7)	1.4 (0.8)
antiviral therapy	146/157(93%)	10.3 (9.7)	1.1 (0.6)	1.5 (0.6)

Table 6. Fever duration and antiviral therapy

			Fever duration, mean (SD), days			
Age	Antiviral therapy	n	>38.0℃	*P value	>37.5℃	*P value
<7yr	started within 24 hr	43	1.2 (0.5)	0.058	1.4 (0.5)	0.122
	started over 24 hr	8	1.7 (0.7)		1.9 (0.9)	
7-13yr	started within 24 hr	58	1.1 (0.6)	0.209	1.5 (0.6)	0.003
	started over 24 hr	12	1.4 (0.7)		2.1 (0.6)	

*Determined by Mann-Whitney's u-test

respectively, which were shorter than the durations of 2 and 3 days reported in Japan [3] and China [6], respectively. Duration of loss of appetite and staying in bed was approximately 1 day. Therefore, patients may feel sick for the initial 1 or 2 days. Age was also an important factor, as older patients recorded shorter durations of fever.

Cough was a prominent feature, as 96% of the patients had cough in our study. On the first day of pyrexia, 131 patients (83%) already had cough, of which it was severe in 51 (31%) patients. Furthermore, cough was present 2 and 3 days prior to onset of fever in cases reported from Kobe, Japan[3]. One of the characteristic features observed for 2009 H1N1 virus infection was rapidly progressing diffuse severe viral pneumonia with severe hypoxemia affecting young adults with no known coexisting condition [7, 8]. Our findings indicate that cough is a clinical feature even in a mild form of 2009 H1N1 virus infection.

Diarrhea was observed in 38% of the patients compared to vomiting in 18%. Gastrointestinal symptoms were more common for pandemic influenza than for seasonal influenza, as observed in other studies [9].

Delirious behaviors were observed in 15% of patients. No patient developed encephalitis, and the symptoms were transient in our study. Yokota et al reported that encephalitis occurred in 10.5% of patients with influenza in the 2005/2006 season [5]. With respect to the 2009 H1N1 virus infection, 220 patients with influenza-associated encephalopathy were reported in Japan [10]. Delirious behaviors can be common even in a mild form of 2009 H1N1 virus infection.

Fever duration for patients who did and did not receive medication could not be compared because antiviral medication was given to the majority of the patients (93%). However, the patients who received treatment within 24 hours tended to have shorter fever duration than those who received treatment after 24 hours, which were statistically significant in the 7-13 year age group with the difference in fever duration of 0.6 days (p=0.003). The antiviral drugs for influenza usually reduced the duration of disease by 0.5 to 1.5 days in seasonal influenza [11]. In our study, fever duration was particularly shorter than that of seasonal influenza. It took average 37 hours for the patients with seasonal influenza before their body temperature returned to normal following administration of 150 mg of oseltamivir [12]. Hibi et al. also reported that patients with 2007 seasonal influenza A who were treated with oseltamivir recovered within 36 hours after treatment [13]. However, the initial fever stage prior to administration of antiviral medicine was not included in these studies [12, 13]. In contrast, our patients with H1N1 influenza suffered from hyperpyrexia only for 36 hours from the first fever elevation to resolution. These findings strongly suggest that our patients with H1N1 influenza recovered from the illness approximately 12 hours earlier compared to the abovementioned cases with seasonal influenza treated with oseltamivir. A comparison study between 2009 H1N1 virus infection and seasonal influenza in previously healthy children managed in the outpatient settings without antiviral therapy showed that 2009 H1N1 virus infection was an uncomplicated respiratory illness and no more severe than seasonal influenza [14].

The Japan Association for Infectious Diseases recommended antiviral drugs for everyone with 2009 H1N1 virus infection [15]; these drugs can prevent complications such as pneumonia [12, 16]. Cases of H1N1 influenza complicated by pneumonia which were admitted to an ICU or died were less likely to have received antiviral treatment within 48 hours [17]. In patient with mild 2009 N1H1 virus infection, oseltamivir was effective for prevention of development of radiographically confirmed pneumonia, fever durations and viral RNA shedding [18]. The rates of hospitalization and death in the 2009 H1N1 virus infection were substantially lower in Japan than in other countries [19]. One of the reasons may be due to the early institution of antiviral drugs. However, the extensive use of antiviral drugs always carries a risk of development of drug resistance. Oseltamivir-resistant 2009 H1N1 viruses were identified but fortunately they were sporadically isolated [20]. Patients requiring hospitalization had rapidly progressing symptoms, and the mean latency of dyspnea from the onset of fever was 17 hours in patients without any chronic medical conditions, and 12.9 hours in patients with asthma [21]. If a

patient is still stable 1 or 2 days after onset, he or she may have a mild clinical course and may not need the antiviral drugs. As we described, the clinical severity of 2009 H1N1 virus infection was mild in our study patients. Jefferson et al. mentioned that neuraminidase inhibitors could not interrupt viral spread and may have a role in reducing symptoms and complications [16], and did not encourage being overly reliant on pharmacological solutions to influenza. Moreover, the uniform use of antiviral drugs for influenza can affect the behaviors of patients and physicians, which may result in premature access to medical resources, excessive use of influenza antigen assays and over-prescription of antiviral drugs. Use of antiviral drugs can be considered individually, according to the clinical situations, as updated recommendations from the advisory Committee on Immunization Practice of CDC mentioned [22].

In conclusion, our outpatients with 2009 H1N1 virus infection had mild clinical courses, with short durations of 1.5 days for fever exceeding 37.5℃ and 1.1 days for fever exceeding 38.0℃. Fever duration was shorter in patients above 13 years of age. The durations of poor appetite of 20% or less and staying in bed were approximately 1 day. Cough was a prominent feature, and delirious behaviors were often observed and were similar to those observed for seasonal influenza.

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