Characteristics of paediatric patients with 2009 pandemic influenza A(H1N1) and severe, oxygen-requiring pneumonia in the Tokyo region, 1 September–31 October 2009

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Few reports describe the features of 2009 pandemic influenza A(H1N1) pneumonia in children. We retrospectively reviewed 21 consecutive children admitted to hospital from September to October 2009 in the Tokyo region. The diagnosis of 2009 pandemic influenza A(H1N1) virus infection was based on positive results of real-time RT-PCR or rapid influenza antigen test. All patients were hospitalised for pneumonia with respiratory failure and severe hypoxia. The median interval from onset of influenza symptoms to admission was 14 hours (range: 5–72 hours) and the median interval from the onset of fever ($\geq 38^{\circ}\text{C}$) to hospitalisation was 8.5 hours (range: 0–36 hours). All patients required oxygen inhalation. Four patients required mechanical ventilation. Chest radiography revealed patchy infiltration or atelectasis in all patients. Antiviral agents and antibiotics were administered to all patients. Antiviral agents were administered to 20 patients within 48 hours of influenza symptom onset. No deaths occurred during the study period. Paediatric patients with this pneumonia showed rapid aggravation of dyspnoea and hypoxia after the onset of influenza symptoms.

Introduction

The 2009 pandemic influenza A(H1N1) infection has already been seen across most of the world. At least 18,449 deaths have been confirmed through 1 August, 2010 [1]. The mortality rate was 7% among 272 hospital patients in the United States (US). Of these, 122 were children and 100 of the 272 had pneumonia. The mortality rate was 17.3% for 168 critically ill patients in Canada, 50 of whom were children, and 119 of whom had pneumonia [3]. The median interval between onset of influenza symptoms and admission to the hospital was three days for US patients and four days for Canadian patients.

In Japan, the total number of patients hospitalised for 2009 pandemic influenza A(H1N1) between 8 May 2009 (the first reported case [4]) and 31 March 2010 was 17,646 [5]. The Japanese population was 127,510,000 as of 1 October 2009 [6]. Therefore, the calculated hospitalisation rate was 0.014%. A survey of influenza virus A(H1) in Japan revealed that the epidemic peak of the season 2009-10 was earlier than that of previous years. In a normal year in Japan, the epidemic season of influenza is from week 47 to week 12 of next year [7] (Figure 1). An overwhelming number of patients were reported this season compared with the previous year. As a result, this year's influenza infection was unique both temporally and quantitatively. In detail, the number of patients started increasing in week 26, surged in week 39, and peaked in week 49 of this season. Our study period was from week 36 to week 44 of 2009, the early phase of the epidemic in Japan.

Of all patients in Japan hospitalised with 2009 pandemic influenza A(H1N1), 79.2% (13,981 patients) were children (under 15 years of age) [5]; this number was higher than those reported in other countries [2,3,8]. A total of 198 deaths were caused by this influenza infection [9], including 38 paediatric cases. The hospital mortality rate for all age groups was 1.1%, which was markedly lower than 7% that reported in the US [2]. The hospital mortality rate for children was 0.27%, which was lower than that of adult cases. The Japanese Ministry of Health, Labour and Welfare reported that 1,002 cases with severe symptoms were admitted to the intensive care unit (ICU) and 763 cases required mechanical ventilation [5]. Although children are considered to be more vulnerable to pandemic influenza pneumonia, few reports describe the characteristics of this pneumonia in paediatric patients [10,11].

FIGURE 1

Weekly reports of influenza virus A(H1), Japan, 2005–6–2009–10

This season's epidemic peak occurred earlier than in previous years.

TABLE 1 - PART 1

Characteristics of children hospitalised with 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September–31 October 2009 (n=21)

Patients	Age	Sex	Previous significant medical history	Time from onset of illness to admission (hours)	Time from onset of fever up to admission (hours)	Body temperature upon admission (oC)	Duration of hospital stay (number of days)	In need of intensive care yes/no (number of days)	In need of oxygen yes/no (number of days)	In need of mechanical ventilation yes/no (number of days)	Time from onset of illness to intubation (hours)
1	4	M	-	5	5	38	7	Yes (5 days)	Yes (5 days)	Yes (4 days)	7
2	5	F	-	12	12	37.3	12	Yes (8 days)	Yes (8 days)	Yes (7 days)	12
3	7	M	F.C.	5	5	38.1	15	Yes (3 days)	Yes (11 days)	Yes (8 days)	3
4	9	M	K.D.	24	2	39.8	17	Yes (7 days)	Yes (9 days)	Yes (7 days)	0.5
5	5	M	-	14	6	37.3	6	No	Yes (4 days)	No	-
6	5	M	F.C.	8	2	38.6	6	No	Yes (5 days)	No	-
7	5	F	Asthma	12	9	38.5	9	No	Yes (7 days)	No	-
8	5	M	A.B.	24	16	39	7	No	Yes (3 days)	No	-
9	6	M	-	72	1	39	8	No	Yes (5 days)	No	-
10	6	F	Asthma	48	36	40.4	6	No	Yes (3 days)	No	-
11	6	M	Asthma	31	22	39.2	6	No	Yes (3 days)	No	-
12	7	F	A.D.	12	2	38	7	No	Yes (5 days)	No	-
13	7	F	-	24	24	38	9	No	Yes (6 days)	No	-
14	7	F	Asthma	20	5	39.4	6	No	Yes (3 days)	No	-
15	9	F	-	12	22	38.5	9	No	Yes (4 days)	No	-
16	9	M	H.D.	6	7	37.4	7	No	Yes (3 days)	No	-
17	9	M	Asthma	10	10	38	5	No	Yes (2 days)	No	-

18	9	M	Asthma	11	11	39.6	5	No	Yes (3 days)	No	-
19	11	M	Asthma	22	2	39.5	7	No	Yes (5 days)	No	-
20	12	M	A.B.	20	8	39	7	No	Yes (4 days)	No	-
21	15	M	-	24	24	40.1	3	No	Yes (1 days)	No	-
Median (range)				14 (5-72)	8.5 (0-36)	38.8 (37.3-40.4)	7 (3-17)		4 (1-9)		

TABLE 1 - PART 2

Characteristics of children hospitalised with 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September-31 October 2009 (n=21)

Patients	Antibiotics	Antibiotics (macrolids)	Steroid treatment	White blood cell count (/µl) 4000-8000	Lymphocyte count (/µl) 1500-4000	C-reactive protein (m g/d l)<0.3	Creatine kinase (IU/L) 0-160	Lactate dehydro genase (IU/L) 100-225	p H 7.380- 7.460	p CO ₂ 32.0- 46.0	PaO ₂ / FiO ₂
1	ABPC/SBT	AZM	2mg/kg/ day	22,300	892	5.9	543	408	7.17	84	X
2	ABPC/SBT	AZM	pulse therapy	5,400	66	7.9	872	346	7.35	43.9	X
3	ABPC/SBT	CAM	2mg/kg/ day	12,100	370	2.13	76	270	7.404	35.2	X
4	PAPM/BP	AZM	pulse therapy	400	8	0.9	97	299	7.38	36.8	57.9
5	ABPC/SBT	AZM	2mg/kg/ day	13,700	1,370	2.6	123	418	7.313	51	237.8
6	ABPC/SBT	AZM	2mg/kg/ day	19,400	1,552	0.7	81	303	7.408	34.6	104.4
7	ABPC/SBT	AZM	2mg/kg/ day	10,000	160	3.8	75	233	7.418	36.6	183.6
8	ABPC/SBT	AZM	2mg/kg/ day	4,500	873	2.8	131	298	7.438	33.9	262.9
9	ABPC/SBT	AZM	2mg/kg/ day	13,200	528	5.4	172	261	7.36	46.6	219.0
10	CLDM	AZM	2mg/kg/ day	6,400	780	6.2	126	281	7.497	28.7	375.0
11	ABPC/SBT	AZM	2mg/kg/ day	12,300	233	2.3	173	335	7.388	34	104.6
12	ABPC/SBT	AZM	2mg/kg/ day	17,500	350	0.3	102	286	7.391	37.5	134.4
13	ABPC	AZM	2mg/kg/ day	11,600	904	4.8	215	284	7.427	34.1	X
14	ABPC/SBT	AZM	2mg/kg/ day	9,600	691	3.3	194	121	7.356	27.1	346.0
15	ABPC/SBT	AZM	not used	14,170	130	2.9	125	273	X	X	X
16	CTX	AZM	2mg/kg/ day	13,100	1,440	0.4	X	197	7.4	37.7	X
17	not used	AZM	2mg/kg/ day	17,400	175	2.8	285	240	7.35	41.2	X
18	ABPC/SBT	AZM	2mg/kg/ day	6,900	414	0.7	111	245	7.441	34.7	159.0
19	not used	AZM	2mg/kg/ day	9,600	X	5.4	62	233	7.41	37.7	X
20	ABPC/SBT	AZM	2mg/kg/ day	8,800	431	3.6	90	281	7.279	37.4	240.8
21	ABPC/SBT	AZM	2mg/kg/ day	9,900	495	3.9	156	237	7.482	30.7	353.3
Median (range)				11,600	463	2.9	125.5	281	7.4	36.7	219.0
				(400-22,300)	(8-1,152)	(0.3-7.9)	(62-872)	(121-418)	(7.17- 7.50)	(27.1- 84)	(57.9- 375.0)

A.B. Asthmatic bronchitis, ABPC: Ampicillin, ABPC/SBT: Ampicillin/Sulbactam, A.D. Atopic dermatitis, AZM: Azithromycin, CAM: Clarithromycin, CLDM: Clindamycin, CTX: Cefotaxime, F: female, F.C. Febrile convulsion, H.D. Hodgkin's disease, K.D. Kawasaki disease, M: male, PAPM/BP: Panipenem/betamipron, X: not measured

In our institution, we have seen 14 paediatric patients hospitalised for this viral pneumonia since the first case was admitted on 12 September 2009. The period from onset to admission is remarkably shorter than

in previous reports [2,3,8,12]. Despite some serious cases requiring ventilation, no deaths occurred. In this report, we investigated clinical findings, laboratory data including chest radiography and computed

FIGURE 2

Typical chest radiography findings seen in two cases of 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September-31 October 2009

A1

B1

A2

B2

A1 (upper left panel): At the time of admission, patient A's left lung field volume was decreased and left upper lobe showed atelectasis. The patient's right lung had compensatory hyperinflation and the right upper lobe showed interstitial shadow enhancement. B1 (lower left panel): At the time of admission, all of patient B's lung fields showed interstitial shadow enhancement. Atelectasis and infiltration were seen in the right lower lobe. A2, B2 (right panels): Chest radiographs of both patients one month after discharge were normal.

tomography (CT) findings, and medical treatments in paediatric patients with this pandemic influenza pneumonia.

Methods

Subjects consisted of 21 consecutive children (under 15 years of age) who were hospitalised between 1 September and 31 October 2009 with pneumonia caused by 2009 pandemic influenza A(H1N1). The reason for admission was respiratory failure with hypoxia requiring oxygen inhalation in all patients. The 21 cases investigated and included in the present study were hospitalised in three neighbouring institutions in the Tokyo region, the National Defense Medical College Hospital, the National Centre for Child Health and Development, and the Kawaguchi Municipal Medical Centre.

The diagnosis of 2009 pandemic influenza A(H1N1) was based on influenza-related symptoms, such as fever, cough, joint pain, muscle pain and general fatigue, and a positive result of either of a real-time RT-PCR or a rapid influenza antigen test. The former test was performed at regional public health centres using standard primers, and the protocol was provided by the National Institute of Technology and Evaluation and the National Institute of Infectious Diseases of Japan [13]. The latter test was performed using an immunochromatography kit, ESPLINE Influenza A&B-N (FUJI REBIO Inc. Tokyo). We did not test for the presence of any other viruses. We carried out blood culture for all cases. All patients had dyspnoea combined with hypoxia. The diagnosis of pneumonia was made by auscultation and by chest radiography and CT findings.

Data were collected by retrospective review of hospital records by each physician, including clinical course, laboratory data on admission, chest radiography findings, chest CT findings, treatment, and out-

come. Radiologists of each hospital provided the chest radiography and CT findings.

On chest radiographs, interstitial shadow enhancement was defined as a ground glass-like pattern (increased lung field density with visible normal bronchial/pulmonary vascular structures), and atelectasis was defined as consolidation associated with decreased volume of the affected lung segment.

Results

Patients' characteristics

The median age of the children in our study was seven years (range: 4–15 years) and the median body weight was 22.5 kg (range: 17–65 kg). Fourteen of the 21 patients were male.

The median interval from the onset of influenza-related symptoms to admission to the hospital with respiratory failure was 14 hours (range: 5–72 hours) and the median interval from the onset of fever ($\geq 38^{\circ}\text{C}$) to hospitalisation was 8.5 hours (range: 0–36 hours). Nineteen patients were hospitalised within 24 hours of the onset of influenza symptoms, and no patient was hospitalised four or more days after onset.

At admission, all of the patients had marked dyspnoea and hypoxia. Seventeen of the 21 patients had already been given oxygen because of the hypoxia. Mechanical ventilation was required for four cases with severe respiratory failure and was initiated 0.5–12 hours after admission. The median body temperature was 38.8°C (range: 37.3 – 40.4°C) on admission.

The medical history included bronchial asthma in seven patients, asthmatic bronchitis in two patients, febrile convulsions in two patients, and Hodgkin's disease, Kawasaki disease, and atopic dermatitis in one patient each. Seven patients had no underlying diseases.

FIGURE 3

Typical chest computed tomography findings seen in two cases of 2009 pandemic influenza A(H1N1) pneumonia, Japan, 1 September–31 October 2009

A (upper panel): Bilateral lung fields showed interstitial shadow enhancement. B (lower panel): Atelectasis and interstitial shadow enhancement are seen in the bilateral lung fields.

None had had previous severe influenza complications (Table 1).

Examination on admission

The rapid influenza antigen test was positive in 20 of the 21 patients. The remaining patient was proven to be positive for 2009 pandemic influenza A(H1N1) using the RT-PCR assay. All 15 patients examined by RT-PCR were positive for 2009 pandemic influenza A(H1N1). The blood cultures of all 21 patients were negative.

The median leukocyte count was 11,600/ μ l (range: 400–22,300/ μ l). The median lymphocyte count, however, was markedly decreased to 463/ μ l (range: 8–1,552/ μ l), with 17 patients having a count $<1,000$ / μ l. Lactate dehydrogenase (LDH) and creatine kinase (CK) levels were normal in most of the patients. The median C-reactive protein (CRP) level was 2.9 mg/dl (range: 0.3–7.9 mg/dl), showing a mild inflammatory reaction. The median arterial pH was 7.40 (range: 7.17–7.50). The median arterial partial pressure of carbon dioxide (pCO₂) was 36.7 mm Hg (range: 27.1–84 mmHg), with 17 patients showing a normal value (≤ 45 mm Hg). The median ratio of arterial oxygen concentration to the fraction of inspired oxygen (P/F ratio), however, was decreased to 219.0 (range: 57.9–375.0), with 10 of 13 patients having lower than normal values (Table 1). In five cases, the P/F ratio was ≤ 200 , which is one of the criteria of acute respiratory distress syndrome defined by the American-European Consensus Conference [14]. Blood cultures were negative in all patients. On chest radiographs and CT, interstitial shadow enhancements or patchy infiltrations/atelectasis were observed in all patients (Figures 2 and 3).

Treatment

All patients required oxygen. None of the patients had received the vaccination against 2009 seasonal influenza or pandemic influenza. Antiviral drugs (oseltamivir) were administered to all 21 patients, 20 of whom received them within 48 hours of the onset of influenza symptoms. In addition, all patients received antibiotics and 19 received combination therapy of two antibiotics. The combination of antibiotics most frequently used, administered to 12 patients, was ampicillin/sulbactam (ABPC/SBT) and azithromycin (AZM). Furthermore, steroid therapy was given to 20 patients.

As mentioned above, four patients required mechanical ventilation; however, none of the patients received nitric oxide or extracorporeal membrane oxygenation.

Clinical course and outcome

No deaths occurred during the study period and no respiratory sequelae were observed. The median hospital stay was seven days (range: 3–17 days) and the median duration of oxygen therapy was four days (range: 1–9 days) (Table 1). Fourteen patients received physical examinations and chest radiographs at one month after discharge. No abnormal shadows were seen, nor was any deterioration of the patients' physical condition observed (Figure 2).

Discussion

We observed a large number of hospitalisations for 2009 pandemic influenza A(H1N1) pneumonia during the 2009–10 season in our hospital, while no seasonal influenza pneumonia had been observed in the previous year. There were differences to the previous sea-

TABLE 2

Comparison of 2009 pandemic influenza A(H1N1) virus infections in Japan in the period 1 September–31 October 2009 with reports from other countries

Patients	Australia / New Zealand	United States	Canada	Mexico	This study	Japan
Clinical setting	Intensive care	Hospitalised	Intensive care	Intensive care	Hospitalised	Surveillance hospitalised
Study period	1 June to 31 August 2009	1 May to 9 June 2009	16 April to 12 August 2009	24 March to 1 June 2009	1 September to 31 October 2009	Up to 31 March 2010
Number of total cases reported	722	272	168	58	21	17,646
Number of total cases with pneumonia	499	100	119	—	21	—
Number of paediatric cases reported	—	122 (<18 years-old)	50 (<18 years-old)	2 (<15 years-old)	21 (<15 years-old)	13,981 (<14 years-old)
Number of children with pneumonia	—	—	—	—	21	—
Time from onset of illness to admission (days, median)	4 days	3 days	4 days	6 days	0.54 days	—
Mortality rate (%)	14.30%	7%	17.30%	41.40%	0%	1.10%
Number of patients on oseltamivir treatment (%)	—	200 (75%)	152 (90%)	45 (78%)	21 (100%)	—
Number of patients provided oseltamivir 48 hours or earlier after onset of illness n (%)	—	75 (39%)	a	b	20 (95%)	—
Number of patients provided concomitant antibiotic treatment n (%)	—	206 (76%)	166 (99%)	52 (90%)	21 (100%)	—

a,b: These percentages were presumably low because median time from onset of symptoms to hospitalisation was four (a) and six (b) days.
—: not mentioned.

son not only in the number of hospitalised patients but also in the severity of their symptoms.

The pneumonia seen in this patient group was considered fulminant, because of the short interval between symptom onset and hospital admission with respiratory failure (several hours in most cases). At the present time, it is not known whether this is a new type of pneumonia or whether it is simply due to the physical characteristics of Japanese people in general, children specifically, or our medical system.

According to previous reports on 2009 pandemic influenza, the median interval between symptom onset and hospitalisation was four days (range: 2–7 days) for 722 ICU inpatients in Australia and New Zealand [12], three days (range: 0–18 days) for 272 inpatients in the US [2], four days (range: 2–7 days) for 168 critically ill patients in Canada [3], and six days (range: 4–8 days) for 58 critically ill patients in Mexico [8] (Table 2). The intervals in these reports were longer than that found of our study. A report of 13 children in the United Kingdom (UK) with serious pandemic influenza infection described that four patients were hospitalised within two days after influenza onset [10]. In seven of 36 fatal paediatric cases in the US [11], the interval between symptom onset and hospitalisation was within two days. Generally, this interval is shorter in children than in adults. According to a Japanese Paediatric Intensive Care Unit (PICU) network survey, seven of nine patients with 2009 pandemic influenza pneumonia showed dyspnoea within 24 hours from fever onset [15]. The Japan Pediatric Society reported that 15 of 19 cases of this serious pneumonia also showed respiratory failure within 24 hours from onset of fever according to a nationwide study [16]. These results suggest that a short interval from the onset of symptoms to hospitalisation may be one characteristic of paediatric patients, especially in Japan.

The 2009 pandemic influenza A(H1N1) virus shows a strong affinity for the lower respiratory tract, which is one potential reason why it takes a fulminant course [17,18]. A lack of specific antibodies to this virus, helps it to proliferate rapidly. It may be difficult for antiviral drugs to prevent proliferation of viruses in the lung if they are given after the symptoms have already progressed. However, in the late-onset type of pneumonia, early administration of antiviral agents may prevent further progression of symptoms.

Chest radiographs revealed not only diffuse interstitial changes that are usually observed in patients with viral pneumonia [19] but also patchy infiltration and atelectasis. Although patchy lesions usually suggest bacterial pneumonia [19], bacterial infection was not detected in any of our patients. Similar findings including patchy lesions of infiltration and atelectasis on chest radiography have been reported for pandemic influenza patients [20], and this feature may be a characteristic of this viral pneumonia in contrast to seasonal influenza pneumonia. The 2009 pandemic influenza virus has been reported to show a strong affinity for type 2

alveolar epithelial cells [21]. Consequently, it causes deficiency of pulmonary surfactant, a defect that may lead to chest lesions including atelectasis.

All of our patients had dyspnoea, and blood gas analysis revealed hypoxia without CO₂ retention. Similar findings have been reported elsewhere [20]. Severe lymphopenia was seen in this study (most of the lymphocyte counts were <1,000/μl), a finding that was already reported among serious paediatric cases in the UK [10]. There was a similar report from Mexico describing that the lymphocyte count was decreased in pneumonia patients, especially in serious cases [20]. Lymphopenia may also be characteristic of this disease. It has been reported that H5N1 influenza virus induces lymphopenia [22] and destroys lymphocytes [23], but the cause of lymphopenia associated with 2009 pandemic influenza A(H1N1) pneumonia has not been clarified.

Oseltamivir is considered ineffective if it is administered later than 48 hours after symptom onset [24]. Antiviral therapy was given to only 39% of hospitalised patients in the US within 48 hours of symptom onset [2]. This percentage was also low in critically ill Canadian and Mexican patients, with a median interval between symptom onset and hospitalisation of four days in Canada [3] and six days in Mexico [8] (Table 2). Of the 36 fatal paediatric cases in the US, only four received oseltamivir within two days of symptom onset [11]. In our study, 20 of 21 patients received antiviral therapy within 48 hours of symptom onset. Since this percentage is much higher than those reported previously, early administration of antiviral agents might have improved the outcome of the pneumonia by inhibiting viral proliferation. Furthermore, none of the patients developed late-onset pneumonia that became aggravated beyond four days after influenza symptom onset. We think that our results could be due to early administration of antiviral agents (within 48 hours of onset), which is recommended in Japan [25] and is widely performed at outpatient clinics, although the seasonal influenza vaccination is optional. Therefore, late-onset type pneumonia might have been prevented, as has already been suggested elsewhere [2,3,8,12]. Early treatment with antiviral agents for outpatients and inpatients may lead to good prognoses.

Contrary to what has been reported previously [2,3,12,14,25–27], concomitant bacterial infection was not detected in our patients. We considered these cases as primary viral pneumonia, caused by a virus with high affinity for the lower respiratory tract for which the population did not have specific antibodies. These experiences might be useful information for a clinician encountering a new mutated respiratory virus infection.

None of our cases died and each had a good clinical outcome. According to other reports, the mortality rate was higher for US inpatients (7%) [2], critically ill Canadian patients (17.3%) [3] and critically ill Mexican patients (41.4%) [8] (Table 2). These differences may

be due to the fact that the other studies included both adult patients and those who were hospitalised with other complications of this virus. In addition, disease severity was not taken into consideration in these and our study. As mentioned above, our good results might also be attributable to the inhibition of viral proliferation by early antiviral therapy and the prevention of secondary bacterial infection by antibiotic therapy that were applied in this study.

Conclusion

Contrary to previous reports, the Japanese children in this study had fulminant 2009 pandemic influenza A(H1N1) pneumonia. Each developed dyspnoea soon after influenza symptom onset and showed patchy infiltration and atelectasis on chest radiographs. They also had hypoxia without retention of CO₂ and lymphopenia. Although four patients required mechanical ventilation, no deaths occurred. Early antiviral therapy may have caused these good results.

Limitations

The limitations of this study were as follows: it had a small numbers of subjects and participating institutions, all institutions were in close proximity and not widely distributed. Because three hospitals were referral central hospitals, it is unlikely that only mild cases of pandemic influenza pneumonia presented to these hospitals. Our experience may be not representative of Japan, but similar characteristics were showed at a clinical meeting in Japan. The follow-up period was short, and treatment efficacy was not assessed by a randomised control. We did not test for other viruses.

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