

## Swine influenza A (H1N1) virus infection in infants

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**Abstract** There are few reports on pandemic swine influenza A (H1N1) virus infection in very young infants. We aimed to discuss the clinical characteristics and management of the H1N1 influenza infection in very young infants. Clinical characteristics of ten infants diagnosed with H1N1 influenza virus infection during the 2009 outbreak season in a tertiary neonatal intensive care unit were evaluated. The diagnosis was confirmed by testing of respiratory samples with pandemic H1N1 influenza specific real-time PCR assay. Of the 46 patients with fever or respiratory problems, ten (22%) were diagnosed with H1N1 influenza virus infection during the 2009 (October–December) peak outbreak season. All infants including the preterms were admitted from home, seven (70%) were full-term and three (30%) were preterm. Median age of the patients at admission was 24.5 days. Fever and cough were the most common symptoms. Apnea was the initial symptoms in three patients. Two patients required oxygen support, one of which, a preterm baby, had been mechanically ventilated for 2 days. Mean duration of hospitalization was  $7.8 \pm 4.9$  days. Chest radiography

revealed radio-opacities on both lung fields in six patients. In addition, two patients had co-infection. All patients with proven infection were given oseltamivir medication. Recovery was achieved in all patients with no residual deficits or side effects from the antiviral oseltamivir treatment. The H1N1 influenza virus infection in very young infants appears to be mild to moderate in severity. The outcomes of the infants may be influenced by antiviral therapy. Treatment with antiviral oseltamivir appears to have no major adverse effects.

**Keywords** Swine influenza A (H1N1) virus · Pandemic · Acute respiratory infection · Infant · Oseltamivir · Outcome

### Introduction

Swine influenza A (H1N1) virus is a cause of pandemic acute respiratory tract infection among children and adults that was first reported in Mexico and the Southwestern United States in March 2009. Thereafter, infection with this virus has been reported in almost every country [8, 10, 20, 22]. The spectrum of the disease varies from mild upper respiratory symptoms to severe lower respiratory tract disease with respiratory failure. Despite the rapid spread of the pandemic influenza A virus, most cases did not have a serious course of disease [5, 6]. However, mortality due to pandemic H1N1 influenza has also been reported [21]. About 2–5% of people with laboratory-confirmed infection required hospitalization and most of the hospitalized cases had additional co-morbid disease [4, 20]. Hospitalization rates are highest for children under the age of 5 years, especially those under the age of 1 year. In the United States, among patients who were hospitalized with pandemic influenza, 32–45% were under the age of 18 years [30].

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Because influenza viruses rarely infect very young infants, pandemic planning has focused on adults and older children [13, 17, 23]. Since few reports are available on pandemic H1N1 influenza infection in infants, the objective of this study was to examine the clinical characteristics and management of the disease in very young infants. We also wish to share our clinical experiences on this pandemic H1N1 infection of infants. However, a later pandemic may be different in clinical presentation.

## Patients and methods

### Patients and clinical data

This study included ten infants diagnosed with H1N1 influenza virus infection during the 2009 outbreak season, between October and December 2009, peak period for central Anatolia, in the neonatal intensive care unit (NICU) of Dr. Sami Ulus Maternity and Children's Hospital. After the first cases of the H1N1 influenza virus infection were seen in Turkey, all newborns or very young infants requiring admission to our NICU with the symptoms of fever and/or respiratory problems (such as cough, dyspnea, or apnea) along “flu” season were evaluated for pandemic H1N1 virus infection. All infants diagnosed with community-acquired H1N1 virus infection were included in this observational study. The clinical data, results of laboratory testing and radiological studies, medication administered, and the outcomes of the patients were recorded.

Based on the treatment protocols, oseltamivir medication (2–3 mg/kg twice daily for 5 days) was given to all patients who had a definite H1N1 influenza virus infection [9]. For prevention of transmission within the NICU, in addition to the standard measures, patients were isolated during the hospitalization period and kept under observation in incubators. Although our unit is a family-based care unit, no mothers having any influenza like symptoms were allowed to enter the NICU. Breast milk policy was continued during the clinical course. Standard surgical masks, non-sterile gloves, and gowns were used while handling the babies. Other methods, such as negative pressure isolation for the reduction of virus transmission in hospital, were not used. Other patients in the NICU having any symptoms consistent with nosocomial infection during this period were also investigated for nosocomial H1N1 virus infection.

### Laboratory and radiological studies

Routine laboratory studies (e.g., hemogram, serum biochemistry, C-reactive protein), blood culture, and chest radiography were obtained for all patients. The diagnosis of swine H1N1 infection was confirmed by testing of respiratory samples

(nasopharyngeal and pharyngeal swabs) with pandemic H1N1 influenza specific real-time PCR assay.

A(H1N1)v specific primers were provided from the World Health Organization (WHO), and the in-house PCR procedure was performed [18, 29].

### Statistical analysis

Statistical analyses were performed using SPSS 16.0 for Windows. Data were expressed as mean  $\pm$  SD.

## Results

### Demographic features and clinical findings

During the 3 months of the “flu” season, a total of 46 patients with fever or respiratory problems were evaluated for H1N1 virus infection. Of these, ten patients (22%) were diagnosed with H1N1 influenza virus infection. All infants including the preterms were admitted from home. H1N1 influenza virus infections in these patients did not originate from a peri- or prenatal infection of the mother. Median age of the patients at admission was 24.5 days (range 5–70 days). The youngest was a 5-day-old boy. Eight patients (80%) were male. Seven (70%) were full-term and three (30%) were preterm. Age on admission, birth-weight, and gestational age of the patients are shown in Table 1.

Eight patients (80%) had a household contact for flu like symptoms, and in five of them, the initiator was the mother. Fever and cough were the most common symptoms (70%). Apnea was the initial symptom in three patients. No patient had the symptom of diarrhea, but there was vomiting in one patient. Mean duration of the fever was  $2.14 \pm 0.37$  days. While a cough was present in only five patients on admission, the additional two patients developed it during their clinical course. Two patients required oxygen support (case 1 and 3). Case 3 had been mechanically ventilated for 2 days. The co-morbid conditions, gastro-esophageal reflux, and patent ductus arteriosus were present in case 3. Case 10 was a 5-day-old full-term infant who presented with fever and maculopapular rash. Case 3 and case 5 also had co-infection (Table 1). No nosocomial H1N1 infections were determined during this period.

The mean duration of hospitalization was  $7.8 \pm 4.9$  days (range 4–21 days). Demographic features and clinical findings are summarized in Table 1.

### Laboratory and radiological findings

An elevated CRP level was encountered only in case 3 whose *Klebsiella pneumoniae* was isolated from his tracheal aspirate. His chest radiography revealed diffuse infiltrates

**Table 1** Demographic features and clinical findings of the infants with H1N1 influenza virus infection

Case no.	1	2	3	4	5	6	7	8	9	10
Age on admission (days)	8	28	70	28	30	45	17	21	20	5
Gestational age (weeks)	39	34	32	40	38	30	38	39	40	39
Birth weight (g)	3,180	2,400	1,860	3,130	3,580	1,400	3,700	2,700	3,150	3500
Gender	Male	Male	Male	Male	Male	Female	Female	Male	Male	Male
Flu-like symptoms in family	+	+	+	+	+	-	+	+	+	-
Signs and symptoms										
Fever	+	-	-	-	+	+	+	+	+	+
Cough	+	+	+	+	+ <sup>a</sup>	+ <sup>a</sup>	-	-	+	-
Shortness of breath	-	-	+	+	-	-	-	-	-	-
Nasal discharge	+	+	-	+	-	-	+	-	+	-
Conjunctivitis	-	+	-	-	+	-	-	-	-	-
Lethargy/poor sucking	+	+	+	-	-	-	-	-	-	-
Apnea	-	+	+	-	+	-	-	-	-	-
Rash (maculopapular)	-	-	-	-	-	-	-	-	-	+
Vomiting	-	+	-	-	-	-	-	-	-	-
Creptitant rales	+	+	+	+	+	+ <sup>a</sup>	-	-	-	-
Duration of symptoms (days)	1	2	3	3	1	1	1	1	5	2
Clinical characteristics										
Duration of fever (day)	3	-	-	-	2	2	2	2	2	2
Oxygen requirement	+	-	+ <sup>b</sup>	-	-	-	-	-	-	-
Co-infection	-	-	+ <sup>c</sup>	-	+ <sup>d</sup>	-	-	-	-	-
Co-morbid disease	-	Sec. ASD	GER + PDA	-	-	-	-	-	-	-
Infiltrates on chest radiography	+	+	+	+	+	-	-	-	+	-
Oxygen saturation on admission (%)	82	93	75	98	94	95	94	95	96	96
Laboratory findings										
CRP (mg/L)	1.36	4.66	19.63	1.18	4.55	3.34	5.35	2.18	1.98	4.14
WBC ( $\times 10^3$ cells/mm <sup>3</sup> )	5.6	10.2	12.3	5.6	7.4	4.2	10.6	9.3	12.2	11.9
Antiviral treatment (oseltamivir)	+	+	+	+	+	+	+	+	+	+
Hospitalization period (days)	4	5	21	3	9	7	8	7	7	7
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

Sec secundum, ASD atrial septal defect, PDA patent ductus arteriosus, GER gastro-esophageal reflux, CRP C-reactive protein, WBC white blood cell

<sup>a</sup> Emerged at second day of hospitalization

<sup>b</sup> Mechanically ventilated for 2 days

<sup>c</sup> Secondary pneumonia with *Klebsiella pneumoniae*

<sup>d</sup> Urinary tract infection

on both lung fields. Arterial blood gas analyses were normal in all except two patients with mild hypoxemia. No organ dysfunction was noted in any subject. On chest radiography, there were radio-opacities on both lung fields in six patients (Fig. 1). Laboratory findings are summarized in Table 1.

#### Treatment and outcome

All patients with proven H1N1 infection were given oseltamivir medication in addition to supportive care. Empiric antibiotic treatment was provided to all patients until the first culture results were obtained. In addition, the patients with co-infection received specific antimicrobial therapy. Recovery was obtained in all patients with no residual deficits. No adverse effects of the antiviral oseltamivir treatment, e.g., vomiting, impairment in liver, or renal function were detected in any patients.

#### Discussion

There are few reports on the effects of previous influenza pandemics (1918, 1957, and 1968) on infants. Although influenza rarely causes illness in newborns and very young infants, we know that in 1918 pandemic, infant mortality and preterm delivery was increased [24], but this occurred before the development of modern neonatal intensive care and antiviral and antimicrobial therapy. In our cases, clinical course was mild to moderate in severity and there was no mortality. Nevertheless, there are also reports of severe cases in preterm infants during epidemics, which developed significant lung injury [2, 7, 11, 16, 27]. This is likely to be related to the immature immune function of

preterm infants. In our study, of the three preterm infants, only one (case 3) had a severe clinical picture that necessitated intubation and mechanical ventilation. This may be associated with his co-morbid clinical conditions. But in this preterm baby, it is not clear whether co-morbid clinical conditions and/or co-infection with *Klebsiella pneumoniae* caused the patient to require mechanical ventilation, or whether the H1N1 infection led to co-infection and a requirement for mechanical ventilation. In some papers including different age groups, it is reported that fever is a necessary prerequisite symptom seen in 90% to 98% of cases [12, 20, 24]. The course of the disease in neonates and young infants seems to have some differences when compared with that in other age groups. Symptoms of H1N1 infection in very young infants are not specific in comparison with those in older patients. Very young infants can present without fever but with other non-specific symptoms like apnea. This may be because of the low level of immunity in neonates. As with the present cases, apnea may be the major symptom. Barak et al. presented a 50-day-old, very low-birth-weight premature infant with the unique presenting symptom of apnea [2]. Moreover, fever may be the first symptom, and respiratory symptoms may develop later [14, 28, 30], as seen in 70% of our cases. For this reason, in the “flu” season, infants with non-specific symptoms, especially those who have family or contact history, should be evaluated for influenza infections and be monitored for apnea. Clinicians should therefore be aware of insidious symptoms or signs of the probable infection in infants during a pandemic.

Illnesses caused by influenza virus infection are difficult to distinguish from illnesses caused by other respiratory pathogens based on symptoms alone. In addition, young children are less likely to have typical influenza symptoms (e.g., fever and cough). Infants may present with fever and lethargy, indistinguishable from bacterial sepsis, but may not have cough or other respiratory symptoms or signs [28]. In series including all age groups, the frequency of diarrhea ranged from 3% in Germany to 28% in the UK and 17% in children [12, 19, 29]. In our series, although diarrhea was not present in any patient, there was vomiting in one patient. It is not possible to compare our results with other series because no other series of very young infants has yet been published.

As was observed in our own cases, in cases with H1N1 infection, radiographic findings commonly include diffuse mixed interstitial and alveolar infiltrates, although lobar and multi-lobar distributions occur, particularly in patients with bacterial co-infection. On chest computed tomography images, multiple areas of ground-glass opacities, air bronchograms, and alveolar consolidation, particularly in the lower lobes, are seen [15]. In addition, small pleural effusions may occur in these patients, but this may be due to volume overload or possibly to empyema [30].



**Fig. 1** Note diffuse radio-opacities on both lung fields on chest radiography of case 5 obtained at second day of hospitalization

Children less than 1 year old are also known from previous pandemics to be at increased risk of complications [1]. As with our cases, the outcomes of these infants may have been influenced by antiviral oseltamivir therapy. Although use of oseltamivir in children less than 1 year old with novel H1N1 infection was approved by the FDA for the 2009 pandemic period and the recommended dosage is age-based [18], there is limited data on the safety of oseltamivir (or zanamivir) in this age group. Treatment of seasonal influenza in children less than 1 year old suggests that severe adverse events related to oseltamivir are rare [26]. Although all of our patients received oseltamivir treatment, no adverse effects were seen in any patient.

WHO suggests the use of a simple medical mask when working within a distance of 1 m from a patient with suspected H1N1 infection. Although the United States Centers for Disease Control and Prevention recommends N95 masks, their use is not universal in all countries. Influenza viruses are primarily spread from person to person by respiratory droplets. Isolation of affected infants is recommended by most authors. Since the mode of droplet nuclei spread is unclear, negative pressure isolation is not required [3, 25]. Accordingly, infants with suspected H1N1 infection in our NICU were isolated until the diagnosis was confirmed. To avoid droplet transmission, all health care providers working in the NICU were fit-tested and wore standard surgical masks, non-sterile gloves, and clothes. These standard isolation measures taken in our NICU should prevent nosocomial transmission.

In conclusion, the course of H1N1 influenza virus infection in very young infants appears to be mild to moderate in severity, but co-morbid illness may worsen the clinical course. The outcomes of these infants may be influenced by antiviral therapy. Treatment with antiviral oseltamivir appears to have no major adverse effects. Since symptoms of swine influenza A virus infection in very young infants are not specific, clinicians should be aware of insidious symptoms or signs of the disease during a pandemic especially in infants with contact history.

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