Two seasons' experience with pandemic A H1N1 influenza infection in neonates

Jelena Martic[1], Natasa Savic[1], Borisav Jankovic[1], Jasminka Nedeljkovic[2], Zorika Rakonjac[1], Katarina Pejic[1], Gordana Markovic-Sovtic[1]

[1]Mother and Child Health Care Institute "Dr Vukan Cupic" and [2]Institute of Virology, Vaccine and Sera "Torlak", Belgrade, Serbia. E-mail: jelena@net2yu.net

SUMMARY: Martic J, Savic N, Jankovic B, Nedeljkovic J, Rakonjac Z, Pejic K, Markovic-Sovtic G. Two seasons' experience with pandemic A H1N1 influenza infection in neonates. Turk J Pediatr 2012; 54: 612-616.

There are only a few reports on influenza A H1N1 infection in neonates. In this paper, we present our additional experience on the clinical characteristics, epidemiology and treatment of influenza A H1N1 (2009) infection in 10 newborn infants (aged 9-24 days). Influenza A H1N1 infection was confirmed by real-time reverse transcription-polymerase chain reaction of the nasopharyngeal swab specimens. The majority of neonates presented with fever, respiratory symptoms and lethargy. The respiratory illness ranged from mild symptoms to severe pneumonia requiring mechanical ventilation. Antiviral treatment with oseltamivir was started in five patients (50%). One lethal outcome was observed, while nine patients (90%) had complete recovery. To our knowledge, this is the largest presented series of neonatal cases with different clinical symptoms. We discuss the necessity of initiation of oseltamivir in infants with different clinical features.

Key words: neonate, influenza, H1N1, oseltamivir.

The first two cases of novel swine-origin influenza A H1N1 in children were detected in April 2009[1], but soon this infection spread worldwide, and in June 2009, the World Health Organization (WHO) declared the pandemic of the highest level[2]. By August 2010, when the transition from the pandemic to post-pandemic period was announced, about 18,500 laboratory-confirmed deaths from influenza A H1N1 had been recorded[3]. Analysis of pediatric mortality related to pandemic A H1N1 influenza showed that fatal outcome is more likely in children under the age of one year[4]. Neonates, due to the immaturity of their immune system, could be at high risk for development of severe illness and lethal outcome[5]. However, there are only a few reports on infection with influenza A H1N1 in neonates, and they show that the disease can vary from mild to severe[6-8].

This study is an addition to our previously published work of novel H1N1 influenza infection in neonates, which has been enlarged with experience from the second (2010/2011) pandemic season[8]. To our knowledge, this is the largest presented series of neonatal cases with different clinical symptoms, ranging from non-specific signs of infection or mild respiratory symptoms with spontaneous recovery to severe illness with lethal outcome.

Material and Methods

This study included 10 neonates diagnosed with H1N1 influenza virus infection during two consecutive influenza seasons, October 2009-January 2010 and January-March 2011, in the Mother and Child Health Institute of Serbia, "Dr Vukan Čupić", in Belgrade. All neonates were presented to our emergency department or transferred from secondary level hospitals. Influenza A H1N1 infection was confirmed by real-time reverse transcription-polymerase chain reaction (PCR) of the nasopharyngeal swab specimens. The clinical data, results of laboratory testing and radiological studies, medication administered, and outcomes of the patients were recorded. Based on the treatment protocols, the antiviral agent oseltamivir (2-3 mg/kg/dose twice daily orally for 5 days) was

given to patients whose symptoms persisted for more than 24 hours (h) or immediately in patients with significantly altered clinical condition. Routine laboratory studies (e.g., complete blood count, serum biochemistry, C-reactive protein [CRP]), blood culture, and chest radiography were obtained for all patients. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) v. 12.0 for Windows. Data were expressed as mean or median ± S.E.M. The Student's t-test, ANOVA and $\chi 2$ test were used, and the difference was considered statistically significant at a p value of <0.05.

Results

The greatest number of neonates (4) admitted in February 2011, during the second season of the pandemic A H1N1 influenza. The average age at admission was 19.2±1.6 days (range: 9-24 days). The admitted patients were significantly younger in the second influenza season (January-March 2011) (16.0±2.3 vs. 22.4±1.0 days old, $p<0.05$). Three patients (30%) were male. Seven (70%) were full-term and three (30%) were late preterm. Patient characteristics are summarized in Table I.

Nine patients (90%) had a household contact for respiratory infection, while infection was nosocomial in one (10%). Fever with an average temperature of 38.3±0.1°C was the most common symptom (80%), and one patient (10%) was hypothermic. Respiratory symptoms were present with the same frequency as lethargy or poor feeding (60% of cases). The median duration of symptoms before establishing the diagnosis was 1±0.7 days (range: 1-8 days). Two patients (20%) had leukopenia, and the median white blood cell (WBC) count was $12.4\pm1.5 \times 10^9$/L. An elevated CRP level on hospital day 1 (> 10 mg/L) was encountered in only patient No. 1 (with pre-existing condition), and the median CRP level was 3.9±3.2 mg/L. Four patients (40%) had a pathological finding on chest radiographs: hyperinflation, patchy and linear infiltrates or consolidation. Two patients (20%) had severe illness and required mechanical ventilation (no. 1 for acute respiratory distress syndrome [ARDS], no. 8 for recurrent apneas).

Antiviral treatment with oseltamivir was started in five patients (50%). The other five had mild disease with symptoms lasting less then 24h and whose general condition improved before the result of PCR testing for H1N1 was obtained. No adverse effects of this treatment were noted. Empirical antibiotic treatment was given to all patients until the first culture results were obtained. In addition, the patients with coinfection received specific antimicrobial therapy (patient nos. 1 and 8 for suspected bacterial pneumonia, no. 9 for otitis media and no. 10 for urinary tract infection). The median length of hospital stay was 7.5±2.0 days, and in the group of patients with complications (respiratory insufficiency, respiratory syncytial virus [RSV] coinfection, urinary infection), the hospital stay was significantly longer (18.2±2.1 days vs. 6.3±0.5 days, $p<0.01$). In our group of patients, one lethal outcome was observed, while nine patients (90%) had complete recovery.

Discussion

This study represents our additional experience on the clinical characteristics, epidemiology and treatment of influenza A H1N1 (2009) infection in newborns. Based on insufficient data about oseltamivir treatment in newborns, we discuss the necessity of initiation of oseltamivir in infants with different clinical features.

The majority of neonates in this study presented with fever, respiratory symptoms and lethargy. The respiratory illness ranged from mild symptoms to severe pneumonia requiring mechanical ventilation. There are several reports in the literature on influenza A H1N1 pneumonia in neonates, so our finding of four neonates with radiographically confirmed pneumonia is not unusual in this population. Chest radiographic findings in our patients were similar to previously described cases in which hyperinflation, patchy and linear infiltrates or consolidation was noted[9].

The latest analyses of deaths related to pandemic influenza A H1N1 showed the highest case fatality (151 deaths per 100,000 cases) and population mortality rates (14 per million) for children aged less than one year. For most deaths in children younger than two years, moderate or severe preexisting disorders had been reported[4]. The only case of death in our report was a male neonate with congenital abnormality of the upper respiratory

Table I. Demographic Data and Clinical Characteristics of Newborns with Novel A H1N1 Influenza Virus Infection

Patient Number	1	2	3	4	5	6	7	8	9	10
Month of admission	October 2009	December 2009	December 2009	November 2009	November 2009	January 2011	February 2011	February 2011	February 2011	February 2011
Gender (M/F)	F	F	M	F	F	F	F	M	M	F
Gestational age (weeks)	40	37	40	36/37	39	40	40	35	40	40
Birth weight (g)	3050	2800	2850	2700	3350	2600	3700	2150	3550	3550
Apgar scores	6/8	9/10	8	8/9	9/9	8	9/10	8/9	9/10	8/8
Age on admission (days)	24	24	20	20	24	20	15	14	22	9
Source of infection	Caregiver	Family member	Family member	Family member	Mother	Family member	Family member	Mother	Family member	Mother
Fever (°C)	38.3	38.5	38.8	-	38.0	-	38.5	35.2	38.0	37.8
Respiratory symptoms	+	-	-	+	-	+	+	-	+	+
Apnea	-	-	-	-	-	-	-	+	-	-
Lethargy/Poor feeding	+	-	+	-	+	+	-	+	-	+
Duration of symptoms before diagnosis (days)	5	1	1	1	1	8	1	1	2	2
WBC (x10^9cells/L)	12.5	11.5	3.6	14.6	4.9	12.3	12.8	20.5	13.2	8.5
CRP 1st day/2nd day (mg/L)	34.7/37.2	1.9/4.7	2.0/0.7	7.0/5.8	1.6/0.9	0.8/3.1	8.9/5.5	9.5/20.8	5.0	2.9/1.0
Pathological finding on chest radiography	+	-	+	-	-	+	-	+	-	-
Mechanical ventilation	+	-	-	-	-	-	-	+	-	-
Antiviral treatment (oseltamivir)	+	+	+	-	-	+	-	+	-	-
Complication	ARDS, Renal failure	-	-	-	-	RSV co-infection	-	Respiratory insufficiency, Bacterial pneumonia	Otitis media	Urinary infection, Rotavirus enteritis
Hospital stay (days)	24	7	8	5	5	18	6	17	7	14
Outcome	Death	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

M: Male. F: Female. ARDS: Acute respiratory distress syndrome. CRP: C-reactive protein. RSV: Respiratory syncytial virus. WBC: White blood cell.

tract, which required prolonged mechanical ventilation. The second patient who required mechanical ventilation was a late preterm infant who presented with hypothermia, lethargy and recurrent apneas. Apnea as a symptom of influenza A H1N1 was also reported in three infants (1 of them was premature and required mechanical ventilation) in the study of Zenciroglu and coworkers[10]. Therefore, prematurity as well as comorbidity represent risk factors for severe illness in neonates with influenza A H1N1 infection.

The study of Holgate and coworkers[11] reported the characteristics of three low-birth-weight infants with influenza A H1N1 infection who required increased respiratory support (nasal continuous positive airway pressure [CPAP] in 2 and mechanical ventilation in 1). In two of these infants, RSV coinfection was detected[11]. In our study, one female infant also had RSV coinfection and increased oxygen requirement, and another newborn had rotavirus coinfection. Besides bacterial, viral coinfection must be considered as well in infants with influenza A H1N1 infection.Oseltamivir, a neuraminidase inhibitor, is approved for the treatment and chemoprophylaxis of influenza among children aged one year or older[12]. Although use of oseltamivir in children less than one year old with influenza A H1N1 infection was approved by the Food and Drug Administration (FDA), the Advisory Committee on Immunization Practices, and Centers for Disease Control and Prevention for the 2009 pandemic, there are insufficient data about the safety of oseltamivir in neonates[13,14].

The largest report of oseltamivir use in infants showed that adverse neurological events were not more common in the oseltamivir group compared with other antiviral agents (adamantanes)[15]. Another study found no significant difference in the incidence of the most frequently reported adverse drug reactions (vomiting, diarrhea, ear disorders, and insomnia) in children less than one year and other age groups[16]. Dosing of oseltamivir in neonates and young children is variable, depending on gestational age and body weight, illustrating the need for further pharmacokinetic studies in this population. Meanwhile, careful attention to dosing oseltamivir for neonates is essential.

Some data indicate that antiviral treatment might be effective in reducing morbidity and mortality in hospitalized patients even if treatment is delayed for more than 48h after the onset of illness[13]. Our experience with late onset of therapy in a patient with comorbidity and respiratory symptoms was discouraging. This patient was the first case of documented H1N1 infection in infants in our country, so late recognition of the infection might have contributed to the delayed treatment and lethal outcome.

There is no doubt that prompt initiation of oseltamivir therapy in severely ill neonates and those with pre-existing disorders is strongly recommended. Whether or not the initiation of oseltamivir within the first 24h of onset of influenza-like symptoms is necessary in term newborns in good general condition and without a pre-existing condition remains questionable. Based on our limited experience, these infants could be carefully observed without promptly starting antiviral therapy. Clinical judgment is essential in treatment decisions. Since influenza pandemics are known to recur at intervals of several decades, our experience in treating neonates with influenza A H1N1 infection will be useful in future pandemics.

REFERENCES

1. Swine influenza A (H1N1) infection in two children: Southern California, March–April 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 400–402.
2. World Health Organization. http://www.who.int/csr/disease/swineflu/4th_meeting_ihr/en [DG Statement following the meeting of the Emergency Committee] [Accessed 3 March 2010].
3. World Health Organization. Disease Outbreak News: Pandemic (H1N1) 2009 – update 112. 6 Aug 2010. http://www.who.int/csr/don/2010_08_06/en/index.html
4. Sachedina N, Donaldson L. Pediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. Lancet 2010; 376: 1846-1852.
5. You D, Ripple M, Balakrishna S, et al. Inchoate CD8+ T cell responses in neonatal mice permit influenza-induced persistent pulmonary dysfunction. J Immunol 2008; 181: 3486-3494.
6. Sert A, Yazar A, Odabas D, Bilgin H. An unusual cause of fever in a neonate: influenza A (H1N1) virus pneumonia. Pediatr Pulmonol 2010; 45: 734-736.
7. Jajoo M, Gupta R. H1N1 influenza in a preterm neonate. Indian J Pediatr 2010; 77: 1045-1046.

8. Martic J, Savic N, Minic P, Pasic S, Nedeljkovic J, Jankovic B. Novel H1N1 influenza in neonates: from mild to fatal disease. J Perinatol 2011; 31: 446-448.
9. Lee EY, McAdam AJ, Chaudry G, Fishman MP, Zurakowsky D, Boiselle PM. Swine-origin influenza A (H1N1) viral infection in children: initial chest radiographic findings. Radiology 2010; 254: 934-941.
10. Zenciroglu A, Kundak AA, Aydin M, et al. Swine influenza A (H1N1) infection in infants. Eur J Pediatr 2011; 170: 333-338.
11. Holgate SL, Bekker A, Rabie H, Cotton MF. Oseltamivir use in low-birth weight infants during the 2009 nH1N1 influenza A outbreak in the Western Cape, South Africa. J Trop Pediatr 2012; 58: 102-106.
12. Roche Laboratories Inc. Tamiflu (oseltamivir phosphate) capsules and oral suspension (package insert). Nutley, NJ: Roche Laboratories, Inc; 2009.
13. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM. Antiviral agents for the treatment and chemoprophylaxis of influenza - recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR Surveill Summ 2011; 60: 1-24.
14. FDA Notifications. EUA issued for treating novel 2009 H1N1 Flu. AIDS Alert 2009; 24: 69-70.
15. Kimberlin DW, Shalabi M, Abzug MJ, et al. NIAID Collaborative Antiviral Study Group. Safety of oseltamivir compared with the adamantanes in children less than 12 months of age. Pediatr Infect Dis J 2010; 29: 195-198.
16. Dalvi PS, Singh A, Trivedi HR, Mistry SD, Vyas BR. Adverse drug reaction profile of oseltamivir in children. J Pharmacol Pharmacother 2011; 2: 100-103.