Journal of Perinatology (2011) 31, 446–448

www.nature.com/jp

PERINATAL/NEONATAL CASE PRESENTATION

Novel H1N1 influenza in neonates: from mild to fatal disease

J Martic[1], N Savic[1], P Minic[1], S Pasic[1], J Nedeljkovic[2] and B Jankovic[1]

[1]Mother and Child Health Care Institut, 'Dr Vukan Cupic', Belgrade, Serbia and [2]Institute of Virology, Vaccine and Sera 'Torlak', Belgrade, Serbia

Analysis of pediatric deaths associated with pandemic A H1N1 influenza shows that fatal outcome is more likely in young children, under the age of 5. Neonates, because of the immaturity of their immune system, could represent a high-risk group for severe disease and fatal outcome. We present a group of five neonates with confirmed novel influenza A H1N1 infection. This report indicates that the full spectrum of influenza A H1N1 infection ranging from mild febrile illness with spontaneous recovery to severe disease with fatal outcome may be expected even in neonates.
Journal of Perinatology (2011) **31,** 446–448; doi:10.1038/jp.2010.194

Keywords: neonate; influenza; H1N1; oseltamivir

Introduction

Due to the rapid spread of novel swine-origin influenza A H1N1 virus, the World Health Organization (WHO) in June 2009 declared the pandemic to be one at the highest level.[1] Analysis of pediatric deaths associated with pandemic A H1N1 influenza shows that fatal outcome is more likely in children under the age of 5.[2] Neonates, because of the immaturity of their immune system, could represent a high-risk group.[3] However, reports on infection with H1N1 influenza in neonates are very scarce.

In this paper, we present a group of five neonates with confirmed influenza H1N1 infection that were treated in our hospital from October 2009 until February 2010. According to our best knowledge, this is a unique report focusing exclusively on newborn infants with a broad spectrum of influenza H1N1 disease ranging from non-specific signs of infection or mild respiratory symptoms with spontaneous recovery, to severe illness with lethal outcome.

Case

Case 1

A female, term infant was born by cesarean section due to fetal distress. She received bag and mask ventilation in the delivery room and suffered from recurrent apnea thereafter, requiring mechanical ventilation. After several unsuccessful weaning attempts, the infant was transferred to our hospital for further treatment on the 24th day of life. Immediate flexible bronchoscopy revealed the presence of laryngomalacia, bilateral vocal cord paresis and hypotonia of hypopharyngeal muscles. After 24 h, the newborn became febrile to 38.3 °C, tachycardic, tachypneic and hypoxemic. Because of the possible intrahospital infection, antibiotic therapy (vancomycin and meropenem) was commenced. But, after 48 h cultures of blood, urine and tracheal aspirate were sterile and respiratory syncytial virus antigen was not detected in nasopharyngeal aspirate, so a nasopharyngeal swab specimen for pandemic influenza H1N1 testing was taken. Infection was confirmed by real-time reverse transcription-PCR of the nasopharyngeal swab specimen. Therapy with oseltamivir ($2\,mg\,kg^{-1}$ per dose) was started 72 h after deterioration. On the following days, the baby was still febrile and hypoxemic, with progression of respiratory failure and chest X-ray consistent with development of acute respiratory distress syndrome. In spite of treatment attempts with porcine surfactant, inhaled NO, as well as hemodiafiltration, clinical deterioration progressed, resulting in the patient's death after 3 weeks.

An autopsy revealed diffuse changes in the lung parenchyme with signs of severe interstitial fibrosis, epithelial denudation and squamous metaplasia of the muscular layer in bronchioles, as well as diffuse alveolar damage with marked hyaline membrane formation and bilateral acute bronchopneumonia.

Case 2–5

Another four newborns with infection caused by influenza A H1N1 virus were treated in our hospital from October 2009 until February 2010. Patient characteristics are summarized in Table 1. Two infants were born in late preterm gestation. Three of them were hospitalized because of fever and non-specific symptoms of infection. Only patient 4 had mild respiratory symptoms. Transmission occurred most probably by direct contact with family members or caregivers. Laboratory findings, also presented in Table 1, were consistent with viral infection. All newborns were negative for respiratory syncytial virus infection, but nasopharyngeal swab specimens taken for pandemic 2009

Correspondence: Professor B Jankovic, Mother and Child Health Care Institute, 'Dr Vukan Cupic', Radoja Dakica 6, 11070 Belgrade, Serbia.
E-mail: dulem@net2yu.net
Received 10 October 2010; accepted 24 October 2010

Table 1 Clinical characteristics of newborns with 2009 pandemic influenza A (H1N1) virus infection

Case	*Sex*	*Gestational age at delivery (weeks)*	*Birth weight (g)*	*Apgar scores*	*Age at diagnosis (days)*	*Fever (°C)*	*Other symptoms*	*Source of infection*	*CRP first day/CRP second day ($mg\,l^{-1}$)*	*Leukocyte count per mm^3*	*Oseltamivir ($mg\,kg^{-1}$ per dose)*
2	F	37	2800	9/10	24	38.5	—	Caregiver	1.9/4.7	11.5	3.6
3	M	40	2850	8	20	38.8	Lethargy, poor feeding	Family member	2.0/0.7	3.6	3.5
4	F	36/37	2700	8/9	20	—	Cough, sneezing	Family member	7.0/5.8	14.6	—
5	F	39	3350	9/9	24	38.0	Lethargy, poor feeding	Mother	1.6/0.9	4.9	—

Abbreviation: CRP, C-reactive protein.

influenza H1N1 testing by PCR were positive. Two newborns were admitted in the evening and the results were available early afternoon the next day. At that time both patients were afebrile with improved general condition and therapy with oseltamivir was not started. In the other two patients therapy was started within the first 24 h of hospitalization. The average stay in hospital was 5.5 days (ranging from 4 to 7 days).

Discussion

Although outbreaks in neonatal intensive units have been described during the influenza epidemic, influenza has been an uncommon illness in newborns.[4] Recent animal as well as human infant studies suggest that failure to develop a cytotoxic T lymphocyte response is a possible cause of the high rate of infant morbidity and mortality caused by respiratory viruses.[3,5]

Among the 39 pediatric deaths associated with H1N1 novel influenza infection in the United States, 67% had at least one high-risk medical condition.[2] Our first patient possibly belonged to the high-risk group because of the congenital abnormality of the upper respiratory tract as well as the prolonged mechanical ventilation. Histological analysis on autopsy of the lungs in this patient was consistent with pulmonary pathological findings observed in fatal influenza H1N1 infection in adults.[6] Approximately 30–40% of the fatal cases with H1N1 novel influenza infection have a bacterial coinfection, which was not confirmed in our patient, although clinical, laboratory and autopsy findings suggested a bacterial pulmonary superinfection.

Although transplacental infection during maternal viremia is possible,[7] the most frequent scenario would probably be the transmission by direct contact with family members or caregivers. History of influenza virus infection was positive in all our patients, except for a first patient who had previously been hospitalized at another medical institution. Nosocomial transmission of 2009 H1N1 influenza was already reported in three pediatric patients from Argentina.[8]

In spite of the fact that oseltamivir is approved for treatment and prophylaxis of influenza in children $\geqslant 1$ year of age, only few studies demonstrate its safety in children lesser than 1 year old.[9] The favorable course of illness in neonates with appropriate initiation of antiviral therapy has recently been reported.[7] On the other hand, the same outcome was noted in our two patients with mild disease who did not receive therapy. In the patient with lethal disease, therapy with oseltamivir was started later than the preferred 48 h from disease presentation, when the greatest benefit for reducing the risk of severe disease is expected.[10]

Although we presented a small group of patients, it seems that even in neonates influenza A H1N1 is usually a self-limiting illness, but can cause a severe disease with fatal outcome. Pre-existing co-morbidity might represent a risk for severe disease in neonates with H1N1 infection. There are insufficient data on neonates with

non-specific symptoms or mild influenza A H1N1 disease who did not receive antiviral therapy. According to our limited experience in two previously healthy newborns with mild disease and favorable course of influenza H1N1 infection without antiviral therapy, use of oseltamivir as 'off-label' drug in this group of patients could be questioned.

Conflict of interest

The authors declare no conflict of interest.

References

1 World Health Organization. http://www.who.int/csr/disease/swineflu/4th_meeting_ihr/enDG Statement following the meeting of the Emergency Committee (accessed 3 March 2010).

2 Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection: United States, April-August 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 941–947.

3 You D, Ripple M, Balakrishna S, Troxclair D, Sandquist D, Ding L *et al.* Inchoate CD8+ T cell responses in neonatal mice permit influenza-induced persistent pulmonary dysfunction. *J Immunol* 2008; **181**: 3486–3494.

4 Wilkinson DJ, Buttery JP, Anderson CC. Infuenza in neonatal intensive care unit. *J Perinatol* 2006; **26**: 772–776.

5 Welliver TP, Garofalo RP, Hosakote Y, Hintz KH, Avendano L, Sanchez K *et al.* Severe human lower respiratory tract illness caused by respiratory syncytial virus and influenza virus is characterized by the absence of pulmonary cytotoxic lymphocyte responses. *J Infect Dis* 2007; **195**: 1126–1136.

6 Gill JR, Sheng ZM, Ely SF, Guinee DG, Beasley MB, Suh J *et al.* Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. *Arch Pathol Lab Med* 2010; **134**: 235–243.

7 Dulyachai W, Makkoch J, Rianthavorn P, Changpinyo M, Prayangprecha S, Payungporn S *et al.* Perinatal pandemic (H1N1) 2009 infection, Thailand. *Emerg Infect Dis* 2010; **16**: 343–344.

8 Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N *et al.* Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. *N Engl J Med* 2010; **362**: 45–55.

9 Kimberlin DW, Shalabi M, Abzug MJ, Lang D, Jacobs RF, Storch G *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.

10 Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J *et al.* Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009; **361**: 1935–1944.